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STUDIES ON THE CIRCULATION IN MAN

X. THE BLOOD-FLOW IN THE HANDS IN DISEASES OF THE HEART *

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GENERAL REMARKS

It has been mentioned in the introduction to the last paper[1] that when proper precautions are taken there is a very fair degree of constancy in the results obtained in successive observations on different days on one and the same patient, provided gross changes in his clinical condition are excluded. Accordingly, a marked change in the flow not accounted for by changes in the external conditions, especially in the external temperature, always suggests some decided alteration in the clinical state of the patient. On the other hand, in certain cases, information may be obtained as to the state of the patient; for example, in regard to the lability of his vasomotor mechanism or the power of adaptation of his heart, by purposely changing the external conditions or by taking advantage of changes that have spontaneously occurred, in order to determine their effect on the flow in the hands or feet.

In comparing the flows in the whole series of cases investigated with those in normal persons, one is struck by the fact that while the flow in persons suffering from well characterized pathological changes (compensated valvular lesions, for example) may be of the normal magnitude, having regard to the age of the patient, the room temperature, etc., in a much larger number of cases it is below the normal, often greatly below it. Sometimes there is good evidence that this diminution in the hand or foot flow is the expression of an increased excitation of the vasoconstrictor mechanism as a whole or at least of the portion of it which presides over the cutaneous vessels not necessarily related to any material diminution in the driving power or the output of the heart. In other cases there is good evidence that the diminished flow in the hand (or foot) is in the main the expression of diminished functional capacity on the part of the heart, associated either with engorgement of the veins

* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Paper IX of this series.

and the right side of the heart or with diminution in the filling of the arteries without increased venous pressure. In still other cases evidence may be obtained of a diminished flow in one or both hands or feet, which is solely or mainly a local condition. A local increase in the flow may accompany such conditions as inflammation or vasomotor paralysis.

The question whether the flow in the hands or feet gives any indication of the functional capacity of the heart would be best discussed on the basis of an experimental comparison of the heart output, as determined gasometrically, with the hand flow in normal and pathological cases. Even in the absence of such a comparison, however, it would appear, that where the hand (or foot) flow is not less than normal it is only in exceptional conditions (local vasomotor paralysis of hands and feet?) that any gross error will be made in assuming that the heart is discharging an amount of blood not inferior to the normal. When, however, the flow in the extremities is permanently and decidedly less than normal, several points have to be considered. In many of these cases in which the normal ratio of the hand flow to the foot flow is preserved[2] in spite of the diminution in the flow and in which no anemia is present, there is often good evidence that the lessened driving power of the heart is primarily responsible for the diminished flow. On the other hand, in the anemias[3] the diminution of the flow in the hand and in the skin generally seems to be a compensating mechanism which permits an even increased quantity of blood to be sent by the heart through the lungs.

A marked disturbance of the normal ratio between the hand and foot flow, of course, gives no information as to the functional capacity of the heart, but indicates in the absence of local anatomical changes which might account for the difference (arteritis, paresis, etc.), a change in vasomotor excitability. Usually, this is manifested in a vasoconstriction of the feet, and a foot flow smaller than the normal in comparison to the hand flow. Since the feet are normally but little exposed in comparison with the hands, local vasoconstriction connected with the technic of the measurements is more likely to occur in the feet than in the hands. In various pathological conditions, for instance, fever,[4] where the vasoconstrictor mechanism of the skin is abnormally excitable the tendency of vasoconstriction in the feet on exposure is intensified. For this reason, as well as on account of the inferior flow per unit of volume in the feet, measurements of the hand flow are always to be preferred to measurements of the foot flow when the object is to obtain general information concerning the circulation and not to study local circulatory conditions. A disturbance of the normal ratio between the hand and

2. See Paper VII of this series, Jour. Exper. Med., 1913, xviii, No. 1.
3. Paper VI of this series, Jour. Exper. Med., 1913, xviii, No. 2.
4. See Paper VIII of this series, Jour. of Exper. Med., 1913, xviii, No. 4.

foot flow, due not to vasomotor, but to anatomical causes (arteritis obliterans, for example), would be revealed by the fact that the ratio remains permanently abnormal even when the external conditions, the room temperature especially, are changed so as to abolish vasomotor differences of the lower and the upper extremities, or when this is done by the administration of vasodilator drugs.

A few words are necessary in regard to the classification of the cases dealt with in this paper. Some overlapping between the groups is unavoidable and the attempt has been made to assign each case presenting a complication of lesions to the group in which the factor seemingly predominant in the clinical picture would place it. For example, in the group of myocardial affections, cases are necessarily included in which there were definite and demonstrable valvular lesions. Thus certain cases with mitral stenosis (and insufficiency) are placed in the myocardial group because there is evidence that auricular fibrillation was also present, and that probably this condition with the consequent marked disturbance of the action of the ventricle was at the time of the investigation a more important factor in the clinical situation than the valvular lesion, or at least a factor which differentiated the case from one with the valvular lesion alone, and gave to it an added gravity. Among the few cases classed as arteriosclerosis, a group which might, of course, have been greatly swollen at the expense of the other groups had attention been paid solely to this condition, is one[5] which might also have gone with the valvular lesions. It is included with the cases of arteriosclerosis simply because that condition was extremely marked in the accessible arteries.

I. CONDITIONS IN WHICH SIGNS OF INVOLVEMENT OF THE MYOCARDIUM PREDOMINATED

There is probably no pathological condition of the heart in which such small hand flows are encountered as in this group. While the myocardium is acting well, grave valvular defects may, as is well known, be overcome, and the output remain for long periods quite at the normal level. The results of the blood-flow measurements in many cases of valvular lesions with good compensation are perfectly normal. With a heart whose myocardium is seriously crippled, even when the valves are anatomically and probably functionally intact, the hand flow may sink to astonishingly small figures. Nor is this difficult to understand. A pump with somewhat leaky valves may still deliver a good stream when the strokes are strong and regular. No matter how tight the valves are the output will be small if the stroke is feeble, uncertain and irregular.

5. Fred. S., Paper XI of this series.

Thus in Stephen F., a man 31 years old, the flow in the hands was only 0.2 gram per 100 c.c. of hand per minute with a room temperature of 23.5 C. increased to 0.5 gram in the right hand during immersion of the left in warm water, or not more than one-twentieth of the normal flow. The protocol of this case has already been published.[6]

The man, a contractor in a small way for brick and carpenter work, was examined in the dispensary and was admitted the same day to Lakeside Hospital where he died a few days later. He stated that between three and four years previous to admission he became ill after a heavy lift and had never been well since. All the signs of cardiac failure were present. To the left the cardiac dulness extended almost to the anterior axillary line. There was marked arhythmia with numerous premature contractions. For some time past he had been aware of the irregular action of his heart and stated that it sometimes stopped for a beat. The pulse-rate was only 60 (counted at the apex beat with the stethoscope). The neck veins were much engorged in the supine position. There was edema of the feet and ankles. The hands and feet were habitually cold although the weather was mild. The whole surface was pale and cool. There was no indication of valvular lesions. No murmurs were detected during the time the patient lived. The lungs were clear. The clinical diagnosis was myocarditis without valvular lesion. The immediate cause of death was pontine hemorrhage. At autopsy the findings were fibrous myocarditis with relative insufficiency but no valvular lesion, pericarditis, perihepatitis and atrophic cirrhosis of the liver, and acute pulmonary edema.

In Mrs. A., a woman aged 72, who came to the dispensary complaining of palpitation of the heart and irregular pulse, the blood-flow in the left hand came out 0.78 gram per 100 c.c. per minute, and in the right 0.45 gram, with room temperature 22.5 C. It must be taken into account that the hands in this case, being the typical hands of old age, consisted largely of bone, which has a small blood-flow.

The irregularity of the heart has been noticed for the past six years. The heart sounds were clear and no murmurs could be detected, but there was marked arhythmia. The pulse rate was 92 in sitting position. There was no edema, no cough. There was a history of rheumatism at 50 years of age, and again the winter before admission. The hands were very thin and rather cool, although she wore gloves and said they were as warm as usual. A diagnosis of senile heart with chronic myocarditis, arhythmia and arteriosclerosis was made. She continued to come periodically to the dispensary for over four months, still complaining of palpitation although the pulse became more regular.

The difference in the flow in the two hands (it must of course be noted that the accuracy of the measurements is less with these small flows than with normal flows) suggests that the smallness of the flow may be partly due to local vasoconstriction, which is often temporarily unequal for the two hands, and not altogether to the small output of the heart. The question may indeed be raised whether as in the anemias[7] a peripheral constriction may not occur in these cases in the interest of an increased flow through the lungs (and through the brain and other

6. Cleveland Med. Jour., 1911, x, 385.
7. Jour. Exper. Med., 1913, xviii, No. 2.

vital organs). In some ways the question is merely an academic one, since it is well known that in marked anemia the heart muscle may be impaired. It is clear that the percentage content and the total absolute amount of hemoglobin in the blood being normal, there may still be oxygen deficiency if the weakened heart is unable to propel the normal amount of blood from the left ventricle through the systemic vessels to the right side of the heart. On the supposition that the right ventricle could deal with a larger quantity of blood than is actually brought to it, a diminution in the average circulation time of the blood through the systemic path brought about by vasoconstriction confined to or predominating in the periphery might increase the minute volume of the heart. In this case the small hand flow, where the myocardium is seriously damaged, would be due to two things: First, diminished driving power of the heart; and second, constriction of the vessels of the peripheral parts in excess of that which would correspond to the diminished filling of the vessels due to the deficient action of the heart alone. Although the output in such cases as Stephen F. is diminished, it is not conceivable that it is diminished in the same proportion as the hand flow.

Jacob W., a house carpenter aged 59, height 5 feet, 1 inch, weight 173 pounds, was admitted at the dispensary April 4, 1911, suffering from myocarditis with anginal attacks. Six months previously while going to church he was suddenly seized with substernal pain, with great dyspnea. He had to sit down and could not speak. Since that time he has had a spell every morning, lasting two to five minutes and it is getting worse. If the pain is severe the left hand and forearm get dead. Since yesterday he has had palpitation. His general health was good until six months ago. He had rheumatism eighteen years ago. He used to drink beer and whisky moderately and to smoke moderately. He denies lues. Physical examination, cyanosis, some icterus; emphysema; heart generally enlarged; no murmurs. The heart sounds are weak; blood-pressure high; some sclerosis of the arteries. Urine negative.

He came periodically to the dispensary after this. April 24, 1911, his systolic blood-pressure was 190, diastolic 110. April 27, 1911, he had five attacks during the night. May 1, 1911, he had a mild attack while being examined in the dispensary. The pain was felt right beneath the sternum and radiated down the inner side of the left arm and up the neck to the chin. The pulse becomes somewhat smaller during the attack but the rate does not change. The heart is enlarged 4 cm. to the left but not to the right. He is still stout. He is being treated with potassium iodid and sodium nitrite. The blood flow in the hands was examined May 1, 1911. Mouth temperature 37.1 C. Pulse (sitting) 100, and rather small. Hands in bath at 2:44 p. m., in calorimeters at 2:55.* At 3:10 p. m. left hand put into water at 42.9 C. (Table 1.)

Cooling of calorimeters, R., 0.11 degrees in fourteen and one-half minutes; Left 0.14 degrees in twenty-one and one-half minutes. Volume of right hand, 508 c.c., of left hand 486 c.c. The hands were fat.

The flow in the right hand works out at 2.46 grams per 100 c.c. per minute, and in the left hand at 1.96 grams. When the left hand was

* Three thousand and fifteen c.c. of water were put into each calorimeter. In the protocols, unless otherwise mentioned, this was the quantity always used for the hand calorimeters.

immersed in warm water the flow in the right rose to 3.86 grams, a fair reflex vasodilatation. Subsequent immersion of the left hand in cold water caused little change in the flow in the right.

TABLE 1.—Calorimetric Measurements in Case of Jacob W.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:54	29.83	29.91	24.1	3:14	30.12	
2:56	29.81	29.86	.....	3:15	30.14	
2:57	29.82	29.86	.....	3:16	30.18	
2:58	29.84	29.87	.....	3:17	30.20	Room 25.0 C.
2:59	29.87	29.88	24.9	3:18	30.23	
3:00	29.87	29.89	.....	3:19	30.26	
3:01	29.88	29.91	.....	3:20	30.29	At 3:20 left hand put in water at 11.5 C.
3:02	29.89	29.92	.....	3:21	30.32	Room 25.1 C.
3:03	29.89	29.92	.....	3:22	30.34	
3:04	29.91	29.93	25.0	3:23	30.36	
3:05	29.92	29.94	.....	3:24	30.39	
3:06	29.93	29.94	.....	3:25	30.41	
3:07	29.95	29.95	.....	3:26	30.44	
3:08	29.98	29.97	.....	3:27	30.47	Left hand dried and wrapped.
3:09	29.99	29.98	.....	3:28	30.49	Room 25.1 C.
3:10	30.02	30.00	.....	3:29	30.51	
3:11	30.03	.....	.....	3:30	30.54	Hand out of calorimeter at 3:30.
3:12	30.05	.....	.....	3:31½	.....	Temp. of L. is now 29.86 C.
3:13	30.08	.....	25.2	3:44½	30.43	Temp. of L. is now 29.76 C.

In James M., a man 60 years old, with a very irregular pulse, enlarged heart and a history of edema of the feet and legs, the flow was 1.99 grams per 100 c.c. per minute in the right hand, and 1.35 grams in the left (for the last ten minutes in the calorimeters). Anemia was probably not an important factor in the small blood-flow, since the hemoglobin content of the blood was 80 per cent. three days before the examination. The calculated flows for the last twenty minutes in the calorimeters are 1.56 grams per 100 c.c. per minute and 1.06 grams for the right and left hands respectively, the ratio between the flows being precisely the same as for the last ten minutes (1.47:1).

James M., a laborer aged 60, was admitted to the City Hospital June 16, 1912. Three weeks before when in another hospital his feet and legs swelled and pitted on pressure. On admission to the City Hospital petechiae were present on both legs but there was no edema. The right side of the chest lags in inspiration and shows diminished resonance beginning at the sixth interspace in the axillary line, and also posteriorly. Fifteen months ago he had dyspneic attacks and the right pleural cavity was tapped. June 21, 1912, the right chest was aspirated but no fluid was obtained. The left border of heart dulness is outside the nipple line, the right border at the right margin of the sternum. The first sound is roughened. Pulse irregular, arhythmic, fair volume, sclerosis marked. The rectal temperature since his admission has varied from 100.4 to 98.2 F.

Examination of the blood-flow in the hands was made June 27, 1912, on which day he was discharged. Hands in bath at 1:34½ p. m.; in calorimeters at 1:43¾ p. m., and out of calorimeters at 2:15.

TABLE 2.—Calorimetric Measurements in Case of James M.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
1.43	31.02	31.12	.....	2.01	30.93	30.97	....
1.45	30.99	31.09	.....	2.02	30.93	30.965	....
1.46	30.98	31.08	22.9	2.03	30.93	30.955	23.0
1.47	30.98	31.07	.....	2.04	30.925	30.95	....
1.48	30.975	31.06	22.9	2.05	30.925	30.945	....
1.49	30.97	31.05	.....	2.06	30.93	30.94	23.1
1.50	30.965	31.04	23.0	2.07	30.925	30.935	....
1.51	30.96	31.03	.....	2.08	30.925	30.93	....
1.52	30.96	31.03	.....	2.09	30.93	30.93	23.1
1.53	30.955	31.025	23.1	2.10	30.925	30.93	....
1.54	30.95	31.02	.....	2.11	30.93	30.925	....
1.55	30.95	31.015	.....	2.12	30.925	30.925	....
1.56	30.94	31.005	23.1	2.13	30.93	30.925	23.0
1.57	30.94	31.00	.....	2.14	30.93	30.92	....
1.58	30.94	30.995	.....	2.15	30.925	30.915	....
1.59	30.935	30.99	.....	2.27	30.795	30.78	....
2.00	30.935	30.98	23.2				

Cooling of calorimeters in twelve minutes, R., 0.13 degrees; L., 0.135 degrees. Volume of right hand 368 c.c., of left hand 356 c.c. He is right handed,* wrists very thin, hands skinny. Pulse 87 (sitting). Very irregular. Rectal temperature 37.65 C. Water equivalent of calorimeters with contents, R., 3,389; L., 3,380. Blood-pressure, systolic 149 (palpation), 152 (stethoscope), 72 (sound gone). Another observation, systolic 144 (palpation).

A case diagnosed as auricular fibrillation (in N. P) is included under this heading, although there was a valvular lesion (mitral stenosis) present as well. The case did not come under my observation until the patient had improved considerably under treatment (digitalis), yet even then the flow in the hands was quite small for her age (1.97 grams per 100 c.c. per minute for the right hand, and 1.59 grams for the left for the last eleven minutes in the calorimeters). The small flow agreed with the persistent coldness of the hands and feet. It was not associated with anemia.

N. P., aged 27, was admitted for her present illness to the City Hospital March 12, 1913. (She was first admitted to the hospital April 4, 1910, suffering from rheumatism.) Heart: Apex beat visible in fifth interspace, one finger's breadth outside the nipple line. A presystolic thrill can be felt here. Left border two finger's breadth outside the nipple line; right border at the midsternal line, upper border at third rib. A rough presystolic murmur is heard over a small area at the apex. All over the precordia and transmitted to the axilla and back

* It can always be assumed that a patient was righthanded unless the contrary is stated in the protocols.

is heard a soft systolic murmur. The pulse shows marked arhythmia. Considerable edema. The urine, March 13, 1913, contained neither albumin nor casts. On May 12, 1913, there was some albumin but no casts. Under treatment (including digitalis) the pulse rate diminished. The arhythmia became less marked although it did not disappear, and the edema cleared up. Her appetite continues poor, but she sleeps well and is not troubled with dyspnea in any position. Her hands and feet are always cold. She says she is only really warm when surrounded by hot water bottles. Polygraph tracings from the jugular and radial taken on May 16, 1913, showed the ventricular form of venous pulse, "*a*" waves being absent from the jugular tracing. The rate of the heart in the semi-reclining position was 80 as counted at the apex with the stethoscope, and precisely the same at the wrist. The variation in the duration of successive beats is great. Twelve successive beats were measured in each of two portions of the tracing. In the first series the durations were 1.1, 0.8, 0.9, 0.8, 0.7, 0.65, 0.65, 0.5, 0.6, 0.9, 0.75, 0.9 second, the average being 0.77 second corresponding to 78 beats per minute. In the second series the durations were 0.85, 0.65, 0.75, 0.7, 0.7, 0.55, 0.75, 0.85, 0.9, 0.85, 0.95, 0.85 second, the average being 0.78 second corresponding to 77 beats per minute.

The blood-flow was examined May 12, 1913. Hands in bath at 2:43 p. m.; in calorimeters at 2:54½, and out of calorimeters at 3:16. Mouth temperature 36.3 C. (the thermometer was in five minutes and special care was taken).

TABLE 3.—Calorimetric Measurements in Case of N. P.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.54	31.56	31.41	.....	3.06	31.455	31.28	23.9
2.55	31.53	31.37	.....	3.07	31.45	31.27	....
2.56	31.51	31.36	24.2	3.08	31.45	31.27	....
2.57	31.50	31.355	.....	3.09	31.44	31.26	....
2.58	31.50	31.35	24.1	3.10	31.43	31.255	23.8
2.59	31.49	31.34	.....	3.11	31.43	31.25	....
3.00	31.49	31.33	.....	3.12	31.42	31.24	....
3.01	31.48	31.31	.....	3.13	31.42	31.235	....
3.02	31.46	31.30	.....	3.14	31.41	31.23	....
3.03	31.46	31.29	23.6	3.15	31.41	31.225	....
3.04	31.46	31.285	.....	3.16	31.405	31.215	....
3.05	31.455	31.28	23.9	3.35	31.19	30.995	....

Cooling of calorimeters in 19 minutes, R., 0.215 degrees; L., 0.22 degrees. Volume of right hand in calorimeter 298 c.c., of left hand 276 c.c. Pulse (sitting) 75 in one count, 66 in another, irregular and weak. It is not easy to count the pulse at the wrist because of the variability in the beat. Systolic blood-pressure in right arm 95. Difficult to determine the blood-pressure with the stethoscope.

A man 44 years old (Jacob S.), with mitral stenosis and insufficiency, an irregular heart, and weak and irregular pulse, from a study of whose case a diagnosis of auricular fibrillation was made, had a flow of only 1.97 grams per 100 c.c. per minute in the right hand, and 0.96 gram in the left, with room temperature 22.2 C. The disproportion in the flow in the two hands is associated with old hemiplegia of the left side. Immersion of the right hand in warm water caused a great percentile increase in the flow in the left hand (to 1.54 grams per 100 c.c. per minute for

the first five minutes and 3.86 grams for the next four minutes), although the maximum was still absolutely a small flow. The fair crossed vasomotor reflex from the normal to the formerly paralyzed hand, which had largely recovered, contrasts with the absence of reflex in a case of old hemiplegia where there had been no recovery of the hand.[8]

Jacob S., a tailor aged 44, height 5 feet, 3½ inches, weight 140 pounds, first presented himself at the dispensary Oct. 27, 1910. Three years before he had rheumatism and had "heart trouble" at that time and also pneumonia. Eleven years ago when sitting in a chair he had a left-sided paralysis which came on him suddenly. He lost consciousness. He also had aphasia. He could understand what was said but could not speak. He recovered his speech in two months. The arm and leg recovered slowly. There was no disturbance of sensation at the time of the stroke, but two months later he had loss of sensation so that a pin could be stuck into his arm or leg without his knowing it. He burnt his left elbow severely without feeling it by leaning on a stove. The lines on the left side of the face are not so deep as on the right. He drags the left foot somewhat. The tongue is protruded in the median line. The reflexes are much increased in both upper and lower extremity. Babinski's sign can be obtained on the left side. Touch and pain are normally appreciated on the left side but heat cannot be distinguished over the left arm. The physical signs of chronic bronchitis and emphysema are present. Heart slightly enlarged both to right and left. Pulmonic second sound accentuated. The heart sounds are very irregular both in force and rhythm. Pulse rate 80.

Nov. 5, 1910, a marked presystolic murmur and thrill can be made out.

Dec. 10, 1910, he is very dyspneic and cannot sleep. Ears, fingers, tip of nose and lips are cyanotic. Positive venous pulse in the neck. The heart dulness extends two fingers outside the nipple line on the left side and two fingers outside the sternal margin on the right. There is a sharp first sound preceded by a faint presystolic murmur and followed by a systolic murmur. The pulse is small, irregular and of very poor volume and tension. The left radial pulse is smaller than the right. The liver is increased in size to percussion. He was received into the hospital to-day where he improved. Blood-pressure, systolic 162, diastolic 120. Blood: leukocytes, 10,500; hemoglobin, 90 per cent.

April 11, 1911, he returned to the dispensary in about the same condition as before he entered the hospital. Pulse rapid and irregular.

April 25, 1911, enlargement of the heart and arhythmia is still marked. Knee-jerk much exaggerated on the left side. When he gets out of breath he feels the left hand getting stiff. The difference in size of the two hands is not conspicuous. The great difference in the two arms is in the girth of the shoulders, the left shoulder being much smaller than the right. He cannot completely extend the left forearm on the elbow owing to contracture. Sometimes when he is grasping an object in his left hand the fingers remain closed around it involuntarily and he has to release the object with the other hand. He lost sexual power at the time of the stroke and has not regained it. He has been constipated since the stroke and has had to use cathartics constantly.

The blood-flow in the hands was measured April 25, 1911. Pulse (sitting) 104. Mouth temperature 36.25 C. Hands in bath at 2:31 p. m., in calorimeters at 2:42.

At 2:55 p. m. the right hand was put into water at 43.3 C.

Calorimeter R. was constantly stirred until 3:10 p. m. After this R. and L. were only stirred occasionally. Cooling of R. from 2:55 to 3:10½ is 0.18 degree (in fifteen one-half minutes.) Cooling of R. from 3:10½ to 3:27 (with little stirring) is 0.15 degree (in sixteen one-half minutes.) Cooling of L. from 3:10½ to 3:28 (with little stirring) is 0.16 degree (in seventeen one-half min-

8. Heart, 1911, iii, 81.

utes.) Accordingly with little stirring L. cooled at the same rate as R. We can therefore assume that with constant stirring this would also be true and that the amount of cooling for L. during the observations is 0.18 degree in fifteen and one-half minutes. Volume of right hand 390 c.c., of left hand 378 c.c.

TABLE 4.—Calorimetric Measurements in Case of Jacob S.

Time	Right	Left	Temp. Room C.	Time	Left	Notes
2:41	29.73	29.72	.....	2:58	29.60	
2:43	29.68	29.65	.....	2:59	29.60	Room 22.7 C.
2:44	29.68	29.65	22.0	3:00	29.60	
2:45	29.68	29.64	.....	3:01	29.59	
2:46	29.68	29.64	.....	3:02	29.61	
2:47	29.67	29.63	.....	3:03	29.62	
2:48	29.67	29.63	.....	3:04	29.63	
2:49	29.67	29.62	.....	3:05	29.64	At 3:05 right hand dried and wrapped.
2:50	29.68	29.63	.....	3:06	29.64	
2:51	29.68	29.62	.....	3:07	29.65	
2:52	29.68	29.61	22.4	3:08	29.65	
2:53	29.69	29.61	.....	3:09	29.67	
2:54	29.69	29.60	.....	3:10	29.68	At 3:10 hand out of calorimeter.
2:55	29.70	.....	.....			
2:56	.....	29.60	22.6	3:10½	.....	Temp. of R. is now 29.52 C.
2:57	.....	29.59	.....	3:27	.....	Temp. of R. is now 29.37 C.
				3:28	29.52	

In a third case diagnosed as one of auricular fibrillation (T. F. K.), a man 57 years old, the flow was 4.45 grams per 100 c.c. per minute for the right hand, over an eighteen-minute period, and 5.23 grams for the left hand (ratio of the flows in the two hands 1:1.17). For the last nine minutes of this period, the flows were 6.21 grams and 7.06 grams, respectively, for the right and left hands (ratio of the flows in the two hands 1:1.13). These are fair flows for the man's age, indicating that the heart in spite of the irregular action of the ventricle is maintaining a fair output. This corresponds entirely with the clinical condition at the time of the blood-flow examination. The edema had completely disappeared. There was no dyspnea. The appetite was good and the patient was no longer confined to his bed. Many of the pulse beats at the wrist were of good amplitude, although others were small (Fig. 1), while in the case of N. P. all of the beats were small.

T. F. K., a bricklayer, aged 57, height 5 feet, 9½ inches, weight 140 pounds, was admitted at the City Hospital May 1, 1913. He had typhoid about thirty years ago and rheumatism sixteen or eighteen years ago. His present illness began last November. His ankles became swollen and also his legs, nearly up to the hips, and he lost strength and weight rapidly. He noticed at the same time that his pulse was irregular. He had pain in the right side of the chest. The swelling in the legs had diminished somewhat before he entered the hospital, but on admission edema and cyanosis were still to be observed. His chest was barrel-shaped with broad costal angle and poor expansion. No râles or dulness over the lungs, but there was a friction rub over the anterior surface of the right

lung. The cardiac impulse was diffuse, and extended considerably beyond the nipple line on the left side. Cardiac dulness enlarged to the left. The liver was somewhat enlarged and pulsation evident in the epigastrium. The veins in the neck were distended. A systolic murmur was heard over the apex. His maximum temperature (on May 9) was 103.6 F., minimum 97.4 on the same day. The maximum temperature on May 16 was 102; May 17, 102; May 19, 101.4 F. The pulse-rate on May 1 was 120; May 19, 92. The pulse-rates were usually above 90. The radial pulse is markedly irregular in amplitude and rhythm, and the irregularity is not affected when respiration is suspended. Polygraph tracings from the distended external jugular vein and the radial artery showed that the venous pulse was of the ventricular character (Fig. 1). Diagnosis, auricular fibrillation. The blood-flow in the hands was examined May 19, 1913, at which time the swelling had entirely disappeared from the lower extremities and the patient was allowed to sit up for a portion of the day. Hands in bath at 3:14 p. m.; in calorimeters at 3:26¾, and out of calorimeters at 3:47.

Fig. 1.—Upper part of tracing, simultaneous record of apex beat and radial pulse. The respiratory movements interfered with the apex trace except towards the end of expiration. At the right is a portion of the apex tracing which allows a sufficiently good comparison to show that some of the apex beats are only feebly represented on the radial trace. The lower portion of the figure gives simultaneous tracings from the external jugular and the radial. As in all tracings, time is marked in fifths of a second. (All tracings reduced to about one-half size of originals.)

TABLE 5.—Calorimetric Measurements in Case of T. F. K.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.26	31.59	31.48	.....	3.38	31.63	31.59	24.0
3.28	31.56	31.46	23.5	3.39	31.66	31.625	....
3.29	31.565	31.47	.....	3.40	31.695	31.665	23.95
3.30	31.57	31.475	.....	3.41	31.72	31.685	....
3.31	31.57	31.48	.....	3.42	31.74	31.73	....
3.32	31.57	31.485	.....	3.43	31.78	31.76	24.0
3.33	31.58	31.50	24.2	3.44	31.79	31.77	....
3.34	31.58	31.50	.....	3.45	31.82	31.82	24.1
3.35	31.59	31.525	.....	3.46	31.84	31.86	....
3.36	31.60	31.55	.....	3.47	31.88	31.90	....
3.37	31.62	31.56	.....	4.16	31.52	31.555	....

Cooling of calorimeters in 20 minutes, R., 0.26 degrees; L., 0.245 degrees. Volume of right hand in calorimeter 444 c.c., of left hand 458 c.c. He is left handed. Water equivalent of calorimeters with contents, R., 3,450; L., 3,461.

Rectal temperature 37.35 degrees. Blood-pressure in left brachial, maximum systolic (when the larger pulsations begin to be heard) 111, 58 (sound gone). Another observation, maximum systolic 114, 58 (sound gone).

In two cases in which acute symptoms diagnosed as due to myocarditis had been present, but which had markedly improved under treatment so that the patients were able to come without trouble to the dispensary, a fair hand flow was found. Both were men 59 years old. In one of these patients (J. S. W.) who had been in the hospital two years before and had been near death, the flow was 6.82 grams per 100 c.c. per minute in the right hand and 6.58 grams in the left, with room temperature at 21.9 C. Simultaneous tracings from the jugular bulb, the radial artery and the apex showed that the *"c"* wave was notably large; the *a* wave was also well marked. All the ventricular beats were recognizable on the radial trace.

J. S. W., a fireman, colored, height 5 feet, 10 inches, weight 160 pounds, born in 1851, was first admitted to the dispensary Feb. 21, 1905, complaining of pain in chest and cough. The heart sounds were faint but clear. No murmurs. Heart dulness enlarged to the left well beyond the mammary line. The pulse was irregular. A diagnosis of myocarditis was made. April 13, 1908, he was again admitted to the dispensary. Heart enlarged to the left two fingers breadth beyond the mammary line. Pulse rapid and irregular. Some albumin in the urine. Nov. 4, 1908, he was admitted to Lakeside Hospital and again on Feb.

TABLE 6.—Calorimetric Measurements in Case of J. S. W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.10	29.40	29.29	.....	3.22	29.96	29.86	....
3.14	29.47	29.38	.....	3.23	30.00	29.91	....
3.15	29.53	29.43	.....	3.24	30.08	29.97	....
3.16	29.59	29.50	.....	3.26	30.20	30.10	....
3.17	29.66	29.55	.....	3.27	30.23	30.12	....
3.18	29.73	29.61	.....	3.34	30.16	30.06	....
3.19	29.78	29.67	.....	3.39	30.09	30.00	....
3.20	29.83	29.71	.....	3.51	29.96	29.88	....
3.21	29.89	29.80	.....				

20, 1909. He had attacks of syncope with fluttering in the chest and came near death. The pulse-rate was 120, systolic blood-pressure 160. Pulse regular and all the beats reached the wrist. Under treatment the pulse rate diminished and as it slowed the arhythmia returned (premature contractions). March 19, 1909, the rate was 68, systolic blood-pressure 160. Tracings from the bulbus venosus showed well marked *a*, *c* and *v* waves of which the *c* wave was very large. Presystolic, systolic and diastolic pulsations were visible over the jugular bulb. He was discharged from the hospital May 5, 1909, improved. Oct. 5, 1909, he reported at the dispensary that he had gained 20 pounds since leaving the hospital. Oct. 4, 1910, he was feeling better, but had occasional smothering sensations. There was now no arhythmia and no albumin in the urine.

The flow in the hands was measured Jan. 10, 1911. He feels much improved. Systolic pressure still very high; when last taken 210. Hands in bath at 3:00 p. m.; in calorimeters at 3:11½, and out of calorimeters at 3:27; 3,050 c.c. of water in each calorimeter. Room temperature 21.7 C. (Table 6.)

Volume of right hand 570 c.c., of left hand 570 c.c. His hands are very large. Pulse 60 (sitting). Mouth temperature 36.5 C. Rectal temperature 37.6 C. Room temperature at end of observations 22.2 C.

Since this time he has continued to report at the dispensary and has been more than once in the hospital with the signs of cardiac breakdown. On Dec. 7, 1912, "the left border of the cardiac dulness is at the anterior axillary line, and the right one finger's breadth beyond the right sternal border, heart thumping and somewhat irregular. Feb. 11, 1913, spitting blood and short of breath. Right border of cardiac dulness two fingers breadth to right of sternal margin. Sounds distant and irregular. No murmurs. Râles throughout both lungs." In June, 1913, eight years from the beginning of his illness, he was still coming to the dispensary and had periods of temporary improvement.

The other patient (Peter B.) was twice examined. At the first examination he had a flow of 6.44 grams per 100 c.c. of hand per minute in the right hand and 5.99 grams in the left, with room temperature 24.5 C. This is by no means a large flow for the temperature, and while fair reflex vasodilatation was obtained by the application of warmth to the contralateral hand, cold did not cause vasoconstriction sufficient to reduce the flow to the initial amount. This agrees well with the fact that arteriosclerosis was distinct, for reflex vasoconstriction is not well obtained in this condition. Almost a month later his hand flow was again measured. He had meanwhile much improved. The flow was 9.95 grams per 100 c.c. per minute for the right and 7.46 grams for the left hand. However, the room temperature was relatively high (26.6 C.), and this probably accounted for a portion of the increase in the flow. The vasodilatation consequent on the high external temperature was considerable and permitted a small reflex vasoconstriction when the contralateral hand was immersed in cold water.

Peter B., a janitor, aged 59, height 5 feet, 2 inches, weight 126 pounds, was under observation at the dispensary with symptoms diagnosed as due to myocarditis. For many years he did heavy work in a gas works. Though his work is now light he has had to give it up for the present. He suffered greatly from rheumatism till about fifteen years ago, since which time he has not been troubled. His joints would swell and he could not walk. He is married and has seven children, all in good health. His present illness dates from somewhat less than two years ago, when he suddenly became unconscious while mowing the lawn. He remained unconscious for five minutes. Three months later he had another attack. He came to the dispensary a number of times, and the records state that he had a slow pulse (60 a minute). The intervals between attacks became gradually shorter, and they occurred about once in six weeks. He falls down and "goes stiff" (extensor spasm) and now he sometimes has two attacks in a week. He seems particularly liable to become unconscious in bed. When he arises after bending down he is blind for about two minutes. Pupil reactions to light and accommodation are normal. He has long suffered from chronic bronchitis. Since the present trouble began his feet are always cold. Previously they used to be very hot and perspired greatly. He does not feel that his hands are cold. Physical examination negative for lungs. Heart dulness two finger's breadth to left of nipple. Sounds clear, distant, the first a little shortened. No accentuation of aortic or pulmonary. Arteries somewhat thickened. Pulse slow, fair volume, well sustained, easily compressible; rate 62. Marked slowing when the vagi are compressed in the neck. There is a venous pulse in the neck.

The flow in the hands was first examined April 21, 1911. Pulse (sitting) 80. Mouth temperature 36.45 C. Room temperature 24.8 C. Hands in bath at 2:31½ p. m., in calorimeters at 2:42. At 2:53 left hand put into water at 42.9 C.

TABLE 7.—Calorimetric Measurements in Case of Peter B.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:40½	30.04	30.03	.....	3:00	30.57	
2:43	30.01	30.02	.....	3:01	30.60	
2:44	30.03	30.03	24.7	3:02	30.63	
2:45	30.06	30.06	.....	3:03	30.69	At 3:03 put left hand in water at 8 C.
2:46	30.09	30.09	.....	3:04	30.71	Room 24.3 C.
2:47	30.11	30.10	.....	3:05	30.77	
2:48	30.14	30.12	.....	3:06	30.79	
2:49	30.17	30.14	.....	3:07	30.81	
2:50	30.20	30.18	.....	3:08	30.83	
2:51	30.24	30.21	24.3	3:09	30.87	
2:52	30.28	30.23	.....	3:10	30.89	
2:53	30.30	30.25	.....	3:11	30.91	At 3:11 dried left hand and exposed it for inspection. Then wrapped it in warm cloth.
2:54	30.32	.....	.....	3:12	30.93	
2:55	30.36	.....	24.4	3:13	30.97	
2:56	30.40	.....	.....	3:14	31.00	Room 24.2 C.
2:57	30.44	.....	.....	3:15	31.04	Hand out of calorimeter at 3:15.
2:58	30.49	.....	24.2	3:30	30.89	At 3:30 temp. L. 29.95 C.
2:59	30.52	.....	.....			

Cooling of calorimeters, R., 0.15 degree in fifteen minutes; L., 0.30 degree in thirty-seven minutes. Volume of right hand 360 c.c., of left 320 c.c. Water equivalent of calorimeters with contents, R., 3,383; L., 3,351.

Second examination May 17, 1911. He is feeling much better than when last examined. He was being treated with potassium iodid and nitroglycerin. Although he has had slight attacks of dizziness and "feeling stupid," he has not fallen or "gone stiff." There is no arhythmia now, nor can any murmurs be detected. Pressure on the vagus in the neck readily inhibits the heart causing the pulse at the wrist to disappear for a beat or two. He feels dizzy during the compression, and he can be made unconscious at any time by pressing on the vagus.

Hands in bath at 2:33 p. m., in calorimeters at 2:43½; mouth temperature 36.5 C.; pulse (sitting) 84. At 2:55 p. m. left hand put into water at 8 C.

Cooling of calorimeters, R., 0.07 degree in ten minutes; L., 0.17 degree in twenty-nine minutes. Volume of right hand in calorimeter 410 c.c., of left hand 394 c.c. The marks were put higher up than usual as his hands were short. The lower mark was about the middle instead of the lower border of the styloid process of the ulna. He seemed gradually to improve and reported at his last visit to the dispensary, June 7, 1911, that he was better. Pulse 84. (See Table 8.)

II. VALVULAR LESIONS

The flow in these cases may be normal or much less than normal, depending on the degree of compensation. Since anemia may be associated with a valvular lesion, it may be a factor in diminishing the hand

flow in the way already discussed in a previous paper.[3] Since, further, the degree of involvement of the myocardium will differ in different cases with one and the same valvular lesion, it is not to be expected that a relatively large flow should always be associated with one particular type of valvular defect and a small flow with another. Nevertheless, so far as can be judged from the series of cases examined, certain of the valve lesions are more apt to be associated with the normal flow than others or even with a flow somewhat above the normal. Mitral insufficiency, for instance, it would seem, is less likely to be associated with a diminished

TABLE 8.—Calorimetric Measurements in Case of Peter B. Second Test

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:43	30.20	30.18	.....	3:00	31.125	
2:45	30.35	30.22	26.4	3:01	31.16	
2:46	30.42	30.27	.....	3:02	31.195	
2:47	30.51	30.32	.....	3:03	31.23	
2:48	30.57	30.38	26.5	3:04	31.29	
2:49	30.63	30.425	.....	3:05	31.325	At 3:05 left hand put in water at 43 C.
2:50	30.68	30.455	.....	3:06	31.355	
2:51	30.73	30.50	.....	3:07	31.38	
2:52	30.79	30.535	.....	3:08	31.41	
2:53	30.835	30.57	.....	3:09	31.44	
2:54	30.88	30.60	.....	3:10	31.475	Room 26.7 C.
2:55	30.915	30.625	.....	3:11	31.505	
2:56	30.94	.....	.....	3:12	31.53	
2:57	30.99	.....	26.8	3:13	31.565	
2:58	31.035	.....	.....	3:14	31.59	Room 26.6 C. Hand out of calorimeter at 3:14.
2:59	31.08	.....	.....	3:24	31.52	At 3:24 temp. L. 30.455 C.

hand flow than aortic insufficiency. In the only case in which a diagnosis of pure aortic stenosis seemed justified, the hand flow was normal, and this agreed with the clinical condition of the patient, who indeed did not enter the hospital for his heart lesion, but for a surgical cause. To emphasize the fact, however, that the mere naming of the valvular lesion is no indication of the amount of the hand flow, we shall begin the description of this group of cases with one of mitral incompetence in which the flow was very markedly diminished.

John T., contractor, aged 28, height 5 feet 6 inches, was admitted to the City Hospital March 31, 1912, with edema of the legs and hands and considerable cyanosis. A systolic murmur can be heard at the apex of the heart. The apex beat is visible and palpable with a heaving impulse in the sixth interspace in the nipple line. There is pulsation in the suprasternal notch. The cardiac dulness in the sixth left interspace is three fingers breadth outside the nipple line. The radial pulse is not easy to feel on account of the edema. It is small in volume and tension but has a regular rhythm. The urine contains albumin. He

was treated with digitalis. April 9, 1912, the blood-flow in the hands was examined. Hands in bath at 2:21 p. m., in calorimeters at 2:31. He had some cough during the observations. Systolic blood-pressure 122. Pulse 70. At 2:47 p. m. left hand put into water at 42.7 C.

TABLE 9.—Calorimetric Measurements in Case of John T.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:30½	31.40	31.49	.....	2:48	31.385	
2:32	31.35	31.44	24.3	2:49	31.385	
2:33	31.35	31.44	.....	2:50	31.39	Room 24.3 C.
2:34	31.34	31.43	.....	2:51	31.39	
2:35	31.34	31.43	24.1	2:52	31.395	
2:36	31.335	31.425	.....	2:53	31.395	
2:37	31.335	31.425	.....	2:54	31.395	
2:38	31.34	31.43	.....	2:55	31.40	Hand out of calorimeter. Room 24.3 C.
2:39	31.345	31.435	.....	3:11	31.23.	At 3:11 temp. L. 31.225 C.
2:40	31.35	31.435	.....			
2:41	31.35	31.435	24.3			
2:42	31.36	31.435	.....			
2:43	31.365	31.44	.....			
2:44	31.37	31.445	.....			
2:45	31.37	31.45	.....			
2:46	31.38	31.455	24.6			
2:47	31.38	31.455	.....			

Cooling of calorimeters, R., 0.17 degree in sixteen minutes: L., 0.23 degree in twenty-four minutes. Volume of right hand 450 c.c., of left hand 438 c.c. Water equivalent of calorimeters with contents, R., 3,455; L., 3,445. Rectal temperature 37.95 C.

April 24, 1912, he was discharged "improved."

In this case the flow was only 2.09 grams per 100 c.c. of hand per minute in the right hand, and 1.67 grams in the left, with room temperature 24.4 C., a flow very much too small for his age.

In a case of mitral stenosis, mitral and tricuspid insufficiency in a man 63 years old (James H.), the flow, measured on an exceedingly hot day with a room temperature of nearly 31 C., was 7.31 grams per 100 c.c. of hand per minute for the right hand and 6.41 grams for the left. Probably not more than one-third to one-half of the flow to be expected in a healthy young adult for that room temperature. Measurements made at such high room temperatures do not lend themselves readily to comparisons. The examination was made on this day purposely to observe the effect of maximal vasodilatation on the flow in this case, since at two previous examinations the hand flow seemed to be greatly diminished by persistent local vasoconstriction which the patient attributed to the low temperature of the wards. He said he had felt chilly all the time, but to-day he felt warm. The pulse showed arhythmia (Fig. 2), partly respiratory.

James H., a hatter, aged 63, admitted to the City Hospital May 2, 1913, suffering from chronic endocarditis with mitral stenosis and insufficiency and tricuspid insufficiency. No history of rheumatism. He complains of weakness and shortness of breath for the last three or four weeks. His feet swell at times. Ears, lips, nails and mucous membranes were markedly cyanotic on admission. There was slight edema of the legs with great varicosity of the leg veins. Marked

Fig. 2.—Tracings from James H.

engorgement and pulsation of the veins of the neck. Lungs revealed nothing special on physical examination. Heart enlarged. Left border of cardiac dulness at the anterior axillary line in the sixth interspace; right border 3 cm. to right of sternum. A presystolic thrill followed by impact and systolic thrill palpable over apex. Liver pulsatile and the lower edge palpable 8 cm. below the costal margin. Radial pulse markedly irregular and arhythmic with fair volume and tension, fairly well sustained. He was discharged May 17 improved. He went to work but became ill again and returned to the hospital May 23, 1913.

TABLE 10.—Calorimetric Measurements in Case of James H.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.00	31.30	31.24	.....	2.17	31.07	30.98	23.3
2.02	31.25	31.17	23.1	2.18	31.055	30.97	....
2.03	31.23	31.16	.....	2.19	31.04	30.96	....
2.04	31.22	31.15	.....	2.20	31.03	30.955	23.4
2.05	31.20	31.13	23.3	2.21	31.02	30.95	....
2.06	31.19	31.12	.....	2.22	31.01	30.945	....
2.07	31.18	31.105	23.3	2.23	31.00	30.94	23.4
2.08	31.17	31.09	.....	2.24	30.995	30.93	....
2.09	31.15	31.08	23.2	2.25	30.995	30.925	....
2.10	31.13	31.06	.....	2.26	30.99	30.915	23.5
2.11	31.125	31.055	.....	2.27	30.98	30.90	....
2.12	31.11	31.05	23.2	2.28	30.975	30.895	....
2.13	31.10	31.04	.....	2.29	30.97	30.89	....
2.14	31.09	31.03	23.2	2.30	30.96	30.88	23.6
2.15	31.08	31.01	.....	3.21	30.395	30.34	....
2.16	31.07	30.99	.....				

The first examination of the hand flow was made on May 29, 1913. His hands were cold when he was brought into the room, having been exposed for some time near an open window. The day, however, was not especially cool. He was allowed to keep the hands wrapped up for twenty minutes in his gown before the observations were begun. Pulse 70 (sitting). The volume of the pulse seemed fair and was thought to indicate a much better flow than was actually shown by the examination, but the veins on the back of the hands, although prominent, filled but slowly when emptied of blood. Hands in bath at 1:50 p. m.; in calorimeters at 2:00½, and out of calorimeters at 2:30.

Cooling of calorimeters in fifty-one minutes, R., 0.565 degree; L., 0.54 degree. Volume of right hand 418 c.c., of left hand 396 c.c. The hands do not feel cold to the touch on coming out of the calorimeters. They are fairly red. The veins on the back of the hand and in the forearm are large, but fill with marked slowness on being emptied. Blood-pressure, left arm, systolic 136, 63 (sound gone). Another observation 134, 68. There was no sensible interval between the change in sound and its disappearance. A few of the larger beats were heard a little before the readings given as systolic pressure. The number of waves coming through increased as the pressure fell.

The flow in the hands in this examination works out at only 0.80 gram per 100 c.c. per minute for the right hand, and 0.64 gram for the left, for the last ten minutes of immersion in the calorimeters. If the whole period in the calorimeters is taken, the calculated flow is still less, as is always the case with a very small flow, the period required for the attainment of the steady state where the thermometers are changing uniformly being long.

A second examination on June 2, 1913, gave an even smaller calculated flow (0.40 gram per 100 c.c. per minute) for the last ten minutes in the calorimeters. The temperature readings followed precisely the same course as at the first examination. The question arises how such small flows can be reconciled with the fairly good volume of the arterial pulse at the wrist. The explanation is found partly in the fact that the venous return was hindered as indicated by the appearance of the veins. The increase in venous pressure while it did not hinder the conduction of the arterial pulse wave, apparently diminished the rate of translation of the blood. A second factor in the small flow was apparently a persistent local vasoconstriction in the hands. That this second factor was concerned is shown by the great improvement in the hand flow at the third examination, although the pulse-rate, far from being accelerated, was even slower than at the previous examinations.

Third examination June 16, 1913. He is feeling well, only weak. No dyspnea and no cough whatever. The day is very warm and the room temperature the highest in the whole series of observations. The veins on his hands and arms fill much more quickly after being emptied than on the two previous occasions. Amplitude of the pulse at the wrist is fair, but not strikingly greater than at the other examinations. Pulse 57 (sitting), with some irregularity but not so marked as before. Hands in bath at 4:06½ p. m.; in calorimeters at 4:15½, and out of calorimeters at 4:27.

Cooling of calorimeters in ten minutes, R., 0.045 degree; L., 0.04 degree. Volume of right hand in calorimeter 408 c.c., of left hand 392 c.c. Water equivalent of calorimeters with contents, R., 3,421; L., 3,409. Blood-pressure in left brachial, systolic 110, another observation 106, 80 (change in sound). Rectal temperature 37.6 C. (See Table 11.)

The general cutaneous vasodilatation at the third examination was evident and is doubtless related to the decidedly diminished systolic pressure. The hands shared in this general vasodilatation, and it is

probable for this reason that the hand flow gives an index to the heart output. Since the hand flow with practically maximal vasodilatation is not half that of a young adult at this room temperature, the heart output is probably at most 50 per cent. of that of a healthy young adult. The three observations together show that in this man of 63 the range of the vasomotor adaptation of the hand blood-vessels is still considerable, a confirmation of his statement that the hot weather suited him.

TABLE 11.—Calorimetric Measurements in Third Examination of James H.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
4.15	31.45	31.50	.....	4.22	31.71	31.72	30.9
4.16	31.46	31.52	.....	4.23	31.765	31.76	....
4.17	31.49	31.54	.....	4.24	31.795	31.83	....
4.18	31.54	31.58	30.8	4.25	31.86	31.84	30.9
4.19	31.58	31.62	.....	4.26	31.89	31.87	....
4.20	31.62	31.655	30.9	4.27	31.925	31.90	....
4.21	31.67	31.69	.....	4.37	31.88	31.86	....

From the standpoint of the technic of the method it ought still to be mentioned that a local vasoconstriction so persistent as not to be overcome during the usual period of an examination (the disappearance of it being shown by a rather abrupt and henceforth steady rise of the thermometers) is rare in hospital cases, although in hands long exposed to cold it may be frequently met with. Where it exists the results cannot, of course, be used as average flows for the patient in question, although the intensity and persistence of the vasoconstriction may be of interest in relation to the patient's condition.

In a case of badly broken compensation in a boy (Joseph Z.), 16 years old, suffering from chronic endocarditis with aortic insufficiency and stenosis and mitral insufficiency, the flow in the right hand was 6.28 grams per 100 c.c. per minute, and in the left hand 4.79 grams. This is much too small for the age of the patient and the very high room temperature (28.1 C.). He was obviously in bad condition. Immersion of the left hand in cold water was followed by but a small diminution of the flow in the right, and immersion of the left hand in warm water by no increase at all, either because the dyspneic condition of the blood caused increased stimulation of the vasoconstrictors of the hand which the vasodilator effect of warmth to the contralateral hand could not overcome, or because the vasoconstrictor tone was already much diminished under the influence of the warm room, although, owing to the handicap of the heart, this was not shown in a large flow. Another possibility is that the dyspneic condition of the blood may have rendered the vasomotor centers less excitable to this form of afferent stimulation.

Joseph Z., boy aged 16, was admitted to the dispensary Nov. 11, 1910, suffering from aortic insufficiency and stenosis with attacks of acute pulmonary edema. He has had rheumatism for ten years. He was in the hospital three weeks for heart trouble which started four years ago. Has dyspnea and weakness. His heart is enlarged 16 cm. to the left, and 5 cm. to the right of the median line. Pulsation in the arteries of the neck. Apex beat heaving. Systolic impulse over apex. A systolic thrill can be felt to the right of the sternum. A double murmur over the apex and louder over the aortic region. Pulse 95. Moderate tension, rather slow rise and quick fall. Pistol shot in femorals. Capillary pulse.

Nov. 15, 1910, he was admitted to the hospital where he improved and after his discharge he remained well, keeping in bed, however, most of the time.

Feb. 2, 1911. When in the dispensary he had an attack of palpitation during which the pulse rate rose to 160, with great throbbing in the carotids and general cyanosis. He began to spit up pinkish frothy liquid. The attack lasted forty-five minutes. He was again admitted to the house, where the diagnosis of chronic endocarditis, mitral insufficiency and aortic insufficiency, was made. He suffered from occasional attacks of tachycardia and shortness of breath. The blood-examination showed hemoglobin 90 per cent. He was discharged July 5, 1911, "improved."

July 14, 1911, he had an attack in the dispensary. There was great pain referred to the right infrascapular region. He received morphin (grain ⅙) and atropin sulphate (gr. 1/300) hypodermically to relieve and calm him, and fifteen minutes later the blood flow in his hands was measured. Pulse (sitting) 140. Hands in bath at 3:01 p. m., in calorimeters at 3:11½. Mouth temperature 38.15 C. At 3:21 p. m. left hand was put into water at 8 C.

TABLE 12.—Calorimetric Measurements in Case of Joseph Z.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
3:11	29.87	29.905	.....	3:27	30.59	
3:12	29.88	29.915	.....	3:28	30.60	Pulse 132.
3:13	29.91	29.93	.....	3:29	30.635	
3:14	29.98	29.97	.....	3:30	30.695	At 3:30 put left hand in water at 43 C.
3:15	30.07	30.04	28.1	3:31	30.735	
3:16	30.13	30.10	.....	3:32	30.775	Room 28.4 C.
3:17	30.21	30.13	.....	3:33	30.81	
3:18	30.22	30.15	.....	3:34	30.87	
3:19	30.27	30.20	.....	3:35	30.895	
3:20	30.29	30.22	.....	3:36	30.93	
3:21	30.32	30.235	.....	3:37	30.975	Room 28.3 C.
3:22	30.34	.....	.....	3:38	31.01	3:38 hand out calorimeter.
3:23	30.37	30.22	.....	3:38½		Temp. of L. 30.16 C.
3:24	30.40	.....	.....	3:48	30.97	Pulse 120. Mouth temp.
3:25	30.49	.....	28.1			38.45 C.
3:26	30.54	.....	.....			

Cooling of calorimeters, R., 0.04 C. in ten minutes; L., 0.06 C. in fifteen one-half minutes. Volume of right hand 406 c.c., of left 412 c.c. He is right handed. Water equivalent of calorimeters with contents, R., 3,420; L., 3,425.

He attended from time to time at the dispensary feeling pretty well for awhile, but compensation broke down again and on March 3, 1913, he had again to seek admission to Lakeside Hospital with the cardiac dulness enlarged to the left to the mid-axillary line.

In another case of aortic stenosis and insufficiency and mitral insufficiency with fair compensation at the time of the blood-flow examination in a man (Matthew K.), 42 years old, the flow was 7.20 grams per 100 c.c. per minute in the right, and 5.49 grams in the left, with room temperature 22.5 C., a flow somewhat below the normal for his age and the external temperature, although by no means remarkably small. He had no edema and no dyspnea, but he complained of pain over the heart and was getting weaker.

Mat. K., aged 42, height 5 feet, 7 inches, weight 165 pounds, a worker in a railway shop, was admitted at the dispensary Dec. 2, 1910, suffering from aortic stenosis and insufficiency and mitral insufficiency. His illness began two months before and he has been getting worse ever since. He feels chilly at times. His weakness is increasing each day and he has had to give up work. He suffers from pain over the heart, palpitation and inability to sleep. There is a probable history of rheumatic fever seven years ago. The left border of the cardiac dulness is 12½ cm. to the left of the mid-sternal line, the right border 4 cm. to the right of it, upper border at third rib. No capillary pulse, no edema, urine normal.

The blood-flow in the hands was measured Jan. 24, 1911. He has no shortness of breath. The systolic blood-pressure is 170. Mouth temperature 36.6 C.; pulse (sitting) 80. Hands in bath at 3:16 p. m.; in calorimeters at 3:27, out of calorimeters at 3:42. There was 3,050 c.c. of water in each calorimeter. Room temperature 22.0 C. before the observations were begun.

TABLE 13.—Calorimeter Measurements in Case of Mat. K.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.26	29.42	29.19	.....	3.37	29.73	29.43	....
3.28	29.40	29.18	.....	3.38	29.78	29.46	....
3.29	29.42	29.18	.....	3.39	29.82	29.48	....
3.30	29.44	29.20	.....	3.40	29.86	29.51	....
3.31	29.47	29.21	.....	3.41	29.90	29.54	....
3.33	29.54	29.29	.....	3.42	29.96	29.58	23.1
3.34	29.60	29.33	.....	3.59	29.76	29.42	....
3.35	29.64	29.37	.....	4.04	29.70	29.37	....
3.36	29.70	29.40	.....				

Cooling of calorimeters in twenty-two minutes, R., 0.26 degree; L., 0.21 degree. Volume of right hand in calorimeter 440 c.c., of left 435 c.c. He is right handed.

He continued to come to the dispensary. On Feb. 2, 1911, he complained of pain over the precordia and down the shoulder and arm. His last visit was on April 2, 1913, when his condition was not essentially altered.

In a case of mitral and tricuspid insufficiency (P. B.) with venous engorgement, edema of the ankles and fluid in the peritoneal cavity, a perfectly good flow was seen in the hands (12.80 grams per 100 c.c. per minute for the right and 13.46 grams for the left, with room temperature 25.5 C.). A fair reflex vasoconstriction was obtained by the application of cold to the contralateral hand, but the application of warmth failed to increase the flow, even to the initial level, owing no doubt to the fact

that the vessels were already so much dilated. There was no dyspnea during the experiment, and the driving power of the heart with its obviously powerful stroke was adequate to maintain a normal flow through the periphery. The vasomotor centers seem to have retained their normal excitability. The cord, therefore, in spite of the venous engorgement, was not suffering appreciably at the time.

P. B., section hand on a railway, aged 31, height 5 feet, 11 inches, was admitted to the dispensary May 12, 1911, with mitral and tricuspid insufficiency. He has been ill for eighteen or nineteen months, during which time he has been unable to work. He had acute articular rheumatism nineteen months before admission, had swollen feet, enlargement of the abdomen and palpitation of the heart and was in bed six weeks. The left border of the cardiac dulness is at the mid-axillary line. There is a large diffuse area of cardiac pulsation visible (positive systolic) and the framework of the chest undulates with each beat. Positive venous pulsation in both jugulars. Liver much enlarged with marked systolic pulsation. There is venous engorgement, edema of the ankles and fluid in the peritoneal cavity.

The blood-flow in the hands was measured May 12, 1912. There was no dyspnea during the examination. Pulse (sitting) 100. Mouth temperature 36.9 C. Hands put into bath at 2:29 p. m., into calorimeters at 2:39. At 2:50 p. m. left hand put into water at 8 C.

TABLE 14.—Calorimetric Measurements in Case of P. B.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:38	30.21	30.11	.....	2:57	31.67	
2:40	30.28	30.19	.....	2:58	31.71	
2:41	30.375	30.28	.....	2:59	31.77	
2:42	30.48	30.40	.....	3:00	31.82	Room 25.7 C.
2:43	30.59	30.495	.....	3:01	31.875	At 3:01 put left hand in water at 43.1 C.
2:44	30.68	30.61	25.5	3:02	31.91	
2:45	30.79	30.71	.....	3:03	31.97	
2:46	30.88	30.80	.....	3:04	32.02	Room 25.5 C.
2:47	30.97	30.875	.....	3:05	32.085	
2:48	31.06	30.96	.....	3:06	32.135	
2:49	31.14	31.06	25.6	3:07	32.195	
2:50	31.23	31.16	.....	3:08	32.26	
2:51	31.295	.....	.....	3:09	32.32	
2:52	31.345	.....	.....	3:10	32.38	3:10 hand out calorimeter.
2:53	31.395	.....	.....	3:10½	.....	Temp. of L. is now 30.98. Room 25.7 C.
2:54	31.475	.....	.....	3:22½	32.25	
2:55	31.545	.....	25.8	3:23½	.....	Temp. L. is now 30.88 C.
2:56	31.605	.....	.....			

Cooling of calorimeters, R., 0.13 degree in twelve one-half minutes; L., 0.28 degree in thirty-two minutes. Volume of right hand 510 c.c.; of left hand 480 c.c.

He entered Lakeside Hospital August 21, 1911. He had then neither cyanosis nor edema, but there was still fluid in the abdomen. The apparent incongruity between the distention of the abdomen, the pulsation of the liver and the great comfort of the patient was remarked. Heart dulness extends on the right to 7 cm.

from the mid-sternal line in the third interspace, on the left to the anterior axillary line in the sixth interspace. The blood examination showed 90 per cent. hemoglobin. He again entered Lakeside Hospital Nov. 2, 1911, and was discharged "improved" Feb. 20, 1912.

The large flow in P. B. contrasts with the small flow in Joseph Z., in whom the delivery of blood to the systemic vessels was seriously interfered with by the insufficiency of the aortic valve.

In Ernest M., another case of mitral insufficiency with chronic bronchitis, in a boy 14 years old, the flow was also good (12.74 grams per 100 c.c. per minute for the right hand and 12.45 grams for the left hand, with room temperature 23.4 C.). Compensation was so far established that he was able to come to the dispensary and had no dyspnea during the examination.

Ernest M., boy, aged 14, height 5 feet, 1¼ inches, was admitted at the dispensary Jan. 26, 1911, suffering from mitral insufficiency with chronic bronchitis. The fingers of both hands show well marked clubbing. He has had a cough ever since he was two years old. He still has the cough and is getting thinner. His arms are thin for his age. He gives a history of heart trouble. He has never been very strong and is not well enough to go to school. His appetite is good. Up to the present time there has never been any blood in the sputum, but on Feb. 7, 1911, he stated that since his last visit he spat some blood. The sputum examination was always negative as regards tubercle bacilli.

The hand flow was measured Jan. 26, 1911. Mouth temperature 38.2 C. Rectal temperature 38.5 C. Hands in bath at 2:56 p. m.; in calorimeters at 3:07, and out of calorimeters at 3:23. There was 3,150 c.c. of water in each calorimeter. Pulse (sitting) 116. The weather was mild with rain. Room 23.4 C.

TABLE 15.—Calorimetric Measurements in Case of Ernest M.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.06	29.71	29.68	.....	3.17	30.18	30.10	....
3.09	29.73	29.68	.....	3.18	30.24	30.16	23.4
3.10	29.77	29.72	.....	3.20	30.34	30.27	....
3.12	29.89	29.82	.....	3.21	30.40	30.33	....
3.13	29.96	29.89	.....	3.22	30.45	30.39	....
3.14	30.00	29.93	.....	3.23	30.50	30.42	23.1
3.15	30.06	29.99	.....	3.42	30.30	30.27	22.7
3.16	30.12	30.05	.....				

Cooling of calorimeters in nineteen minutes, R., 0.20 degree; L., 0.15 degree. L. was on the side of the room next to the radiator, though at a good distance from it. A small centrifuge had been started at 3:23 at the side of the room nearest to R. The difference in the rate of cooling of the calorimeters, which is decidedly greater than usual, may be thus accounted for. Volume of right hand 255 c.c., of left 240 c.c.

In another boy (Frank C.), 17 years old, with mitral stenosis and insufficiency, the flow was also quite normal in amount (11.25 grams for the right and 11.58 grams for the left hand, with room temperature 22.4

C.). Compensation was fairly established. The protocol has already been published.[6] Later he was admitted several times to Lakeside Hospital suffering from broken compensation and was discharged for the last time on March 4, 1912. He afterward died.

One of the most interesting cases was that of Albert H., since the heart underwent rapid deterioration within the period of the observations and the patient died soon after the last examination, when an autopsy was obtained. The patient was a man 31 years of age with a clinical diagnosis of mitral and tricuspid insufficiency, confirmed by the autopsy, which in addition showed pericarditis with large effusion into the pericardial sac. There was no doubt that the myocardium had suffered. The patient suffered much from dyspnea if he attempted to lie down. The flow in the right hand was 4.08 grams per 100 c.c. per minute, and in the left 4.54 grams, with room temperature 24.7 C., a distinctly subnormal flow. Reflex vasoconstriction of the hand was easy to obtain on immersion of the contralateral hand in cold water, but no reflex vasodilatation could be obtained, which agreed well with the obviously poor filling of the vessels of the hand. Ten days later he was again examined. The abdomen was now full of liquid, the legs and feet greatly swollen, the heart-sounds weak and the pulse at the wrists so weak that the heart-rate was counted with the stethoscope. The hands also had increased in size. The blood-flow in the hands was very small and what was considered significant at the time, less than half its amount at the last examination (2.0 grams for the right and 1.88 grams for the left). This was for a period of seven minutes, beginning fifteen minutes after insertion of the hands in the calorimeters. For the first fifteen minutes the flow was still less. The patient said he felt better, but the great decline in the blood-flow was remarked as an ominous symptom. He died in the hospital ten days after the last examination.

Albert H., colored hotel porter, aged 31, was admitted to the City Hospital April 3, 1912, complaining of dyspnea, cough and swelling of the extremities. He had rheumatism three weeks before admission and the legs were very painful. The edema and dyspnea began one week before admission. He has grown worse, coughs most of the time and is very tired on any exertion. The physical signs of fluid in the right pleural cavity are present. Heart dulness, upper border third rib, right border parasternal line, left border midway between nipple and anterior axillary line. The rate of the heart is rapid, the sounds feeble. There is a soft mitral systolic murmur with reduplication of the second sound. Radial pulse small and easily compressible. No fibrosis. Great edema of scrotum and prepuce, and edema of lower extremities. Albumin in urine. April 5 and April 7 the dyspnea and edema were less, the mitral murmur not so pronounced, the pulse soft and not well sustained. April 9, on which day the hand flow was first measured, the signs of an increase in the fluid in the right pleural cavity were present. The heart boundaries were the same as before and the edema was still considerable. Seven hundred and fifty c.c. of liquid was aspirated from the right thorax before the blood-flow examination. His maximum temperature on April 3 was 100.6 F. It rose gradually till April 9 when it reached 104.5 F. The systolic blood-pressure on April 5 was 152; April 7, 160; April 9, 160.

Hands in bath at 1:09 p. m., in calorimeters at 1:19. Mouth temperature 37.8 C. At 1:31 p. m. left hand put into water at 7.9 C.

TABLE 16.—Calorimetric Measurements in Case of Albert H.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
1:18	30.82	30.78	.....	1:35	31.13	
1:20	30.81	30.75	.....	1:36	31.14	
1:21	30.84	30.76	24.6	1:37	31.16	Room 24.7 C.
1:22	30.87	30.79	.....	1:39	31.19	
1:23	30.89	30.82	.....	1:40	31.195	At 1:40 left hand put in water at 43 C.
1:24	30.90	30.85	24.9	1:41	31.21	
1:25	30.96	30.90	.....	1:42	31.22	Room 24.8 C.
1:26	31.03	30.96	.....	1:43	31.23	
1:27	31.07	31.00	.....	1:44	31.245	
1:28	31.08	31.02	24.6	1:45	31.26	
1:29	31.085	31.04	.....	1:46	31.28	
1:30	31.095	31.07	.....	1:47	31.295	
1:31	31.09	31.09	.....	1:48	31.305	
1:32	31.10	.....	.....	1:49	31.325	
1:33	31.105	.....	24.5	1:50	31.33	1:50 hand out calorimeter.
1:34	31.115	.....	.....	1:59	31.23	Temp. of L. is 30.81 C. at 1:59.

Cooling of calorimeters, R., 0.10 degree in nine minutes; L., 0.28 degree in twenty-eight minutes. Volume of right hand 447 c.c., of left hand 450 c.c. He says he does most of his work left handed. Water equivalent of calorimeters with contents, R., 3,452; L., 3,455. Pulse (lying down) 120. Rectal temperature 39.1 C.

April 10 his maximum temperature was 103.8 F.; April 14, 103.3 F. April 17, "the dulness in the right thorax begins as high as the fifth rib posteriorly. Heart boundary is the same." Systolic blood-pressure April 16, 130; April 18, 140; April 19, 130.

Second examination of the hand flow, April 19, 1912. The abdomen now contains much liquid. The legs and feet are greatly swollen and he cannot sleep because he is unable to lie down on account of dyspnea. The heart-sounds are weak and the pulse at the wrist barely discernible. He says he feels better than before the tapping on April 9, but he seems worse than when examined after the tapping on that date. The arms and hands, according to his statement, are not swollen, but simply fat and there is no pitting. Yet measurement of the volume of the hands demonstrates an increase in their size, although the edema is not great enough to be detected by pitting. He has no fever now.

Hands in bath at 1:58 p. m.; in calorimeters at 2:09 p. m., and out of calorimeters at 2:45. At 2:35 the right hand was put into water at 42.7 C.

Cooling of calorimeters, R., 0.295 degree in twenty-eight and one-half minutes; L., 0.17 degree in eighteen and one-half minutes. Pulse 102 (counted with stethoscope). Rectal temperature 37.75 C. It was noticed that he now has piles. He never had them before. Volume of right hand in calorimeter 475 c.c., of left hand 505 c.c. Water equivalent of calorimeters with contents, R., 3,475; L., 3,499. (See Table 17.)

April 26, 1912, edema was general in the legs, arms and face. Maximum temperature 102.4 F. He died April 29. Results of necropsy: Pericarditis; 600 c.c. fluid in the pericardial sac. Mitral valve, edges thickened, insufficient. Tricuspid valve, insufficient. One thousand c.c. fluid in the abdomen. Chronic passive congestion of the liver, spleen and kidneys.

Whether the mere mechanical effect of the liquid in the pericardial sac contributed to the small flow in Albert H. at the second examination cannot of course be determined, although it is likely enough that this was a factor in addition to the weakening of the myocardium and the insufficiency of the valves. However, if the clinical diagnosis in the next case (Roman B.) be accepted, liquid may be present in considerable amount in the pericardial sac without reducing the hand flow very markedly. This patient was a man aged 22, in whom the diagnosis of mitral insufficiency and pericardial effusion was made. Blood-flow measurements in the hands were obtained on three occasions, the first on May 29, 1912, when the heart dulness was much diminished and the

TABLE 17.—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF ALBERT H.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.08	29.81	29.72	.....	2.28	29.66	29.59	....
2.10	29.74	29.67	.....	2.29	29.675	29.61	....
2.11	29.72	29.65	22.7	2.30*	29.685	29.62	....
2.12	29.705	29.635	.....	2.31	29.68	29.61	....
2.13	29.695	29.625	.....	2.32	29.69	29.625	....
2.14	29.69	29.62	.....	2.33	29.695	29.63	....
2.15	29.68	29.61	.....	2.34	29.70	29.63	....
2.16	29.67	29.60	22.5	2.35	29.705	29.635	....
2.17	29.665	29.595	.....	2.36	.....	29.63	....
2.18	29.65	29.58	.....	2.37	.....	29.635	23.5
2.19	29.64	29.575	.....	2.38	.....	29.635	....
2.20	29.635	29.565	22.6	2.39	.....	29.645	....
2.21	29.63	29.56	.....	2.40	.....	29.65	....
2.22	29.625	29.555	.....	2.41	.....	29.655	....
2.23	29.62	29.55	.....	2.42	.....	29.655	....
2.24	29.62	29.55	.....	2.43	.....	29.66	....
2.25	29.63	29.56	.....	2.44	.....	29.665	....
2.26	29.64	29.57	22.7	2.45	.....	29.67	....
2.27	29.65	29.58	.....	3.03½	29.41	29.49	....

* Here the bringing in of the warm water attracted his attention. In excitable patients this may cause a change in the flow.

swelling of the legs present on admission had disappeared. The flow came out 7.61 grams per 100 c.c. per minute in the right hand and 10.59 grams in the left hand, with room temperature 22 C. He seemed fairly comfortable and had no dyspnea. On May 31, when the weather was warmer, the room temperature being 26.3 C., the flow was 8.76 grams for the right hand and 11.05 grams for the left. The average for the two hands is normal, or nearly so, and greater of course at the second examination, in accordance with the increased room temperature. He left the hospital, and after working in a foundry for two days, his legs became swollen and he had to return to the hospital on June 11 with the same

symptoms of broken compensation which he had at first, dyspnea, cough, greatly increased area of cardiac dulness and the edema already mentioned. On June 13 his hand flow was again examined, and came out only 5.52 grams per 100 c.c. per minute for the right hand and 8.74 grams for the left, with room temperature 21.8 C., a considerable smaller flow than at the first examination, although the external temperature was practically the same. The flow, then, concomitantly with the cardiac breakdown, has been decidedly diminished. The marked inequality in the flow in the two hands persists throughout, although the relative difference is greater at the third than at the other two examinations. No local difference in the hands or arms could be discovered to account for the difference in the flows. It is possible that it is connected with intrathoracic changes not taken account of in the diagnosis. The question of differences of flow in the two hands associated with unilateral changes in the lungs and pleurae will be taken up in a future paper.

Roman B., a laborer, aged 22, was admitted to the City Hospital May 17, 1912. He had rheumatism for the first time three years before admission. He has a typical cardiorenal facies. He seems fairly comfortable, with no dyspnea. The heart presents a pear-shaped area of dulness, left border in the mid-axillary line, right border one to three fingers' breadth to the right of the mid-sternal line, making an obtuse cardiohepatic angle. The cardiac dulness is increased when he leans forward. There is a loud systolic murmur at the apex. The second sound in the pulmonic area is split. The sounds are distant. Pulse regular in rhythm, of fair volume, rather rapid rise, and well sustained. Liver three fingers' breadth below costal margin; hard, sharp edge, not tender. Edema of legs. Urine negative.

TABLE 18.—Calorimetric Measurements in Case of Roman B.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.21	31.03	31.05	21.4	3.32	31.52	31.68	....
3.23	31.08	31.09	.....	3.33	31.56	31.74	22.2
3.24	31.12	31.15	21.5	3.34	31.58	31.77	....
3.25	31.19	31.23	.....	3.35	31.60	31.825	22.6
3.26	31.23	31.315	.....	3.36	31.64	31.89	....
3.27	31.28	31.36	.....	3.37	31.68	31.94	22.8
3.28	31.30	31.42	.....	3.38	31.705	31.98	....
3.29	31.36	31.47	21.0	3.39	31.735	32.025	22.5
3.30	31.42	31.56	.....	3.52	31.555	.....	....
3.31	31.48	31.64	21.5	3.52½	.....	31.83	....

Cooling of calorimeters, R., 0.18 degree in thirteen minutes; L., 0.195 degree in thirteen one-half minutes. Volume of right hand 454 c.c. of left hand 439 c.c. He is right handed. Water equivalent of calorimeters and contents, R., 3,458; L., 3,446. Pulse (sitting) 96. Rectal temperature 37.95 C.

May 25, 1912, left cardiac border just outside the nipple line. Right border one finger's breadth outside of sternal margin. Cardio-hepatic angle less obtuse. Liver one finger's breadth below costal border. Heart sounds louder and more distinct.

May 29, 1912, the flow in his hands was measured. Hands in bath at 3:12 p. m.; in calorimeters at 3:21¾, and out of calorimeters at 3:39. Mouth temperature 37.25 C.

Second examination May 31, 1912. He says his right ankle pains him now. It was painful three years ago when he had rheumatism for the first time. Hands in bath at 1:51 p. m; in calorimeters at 2:01½, and out of calorimeters at 2:20.

The weather was considerably warmer than at the last examination.

TABLE 19.—Calorimetric Measurements at Second Examination of Roman B.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.01	31.04	31.03	26.2	2.12	31.52	31.65	26.2
2.03	31.04	31.06	.....	2.13	31.57	31.71	....
2.04	31.08	31.125	26.3	2.14	31.61	31.77	26.3
2.05	31.125	31.17	.....	2.15	31.67	31.85	....
2.06	31.20	31.25	26.4	2.16	31.72	31.925	26.3
2.07	31.27	31.34	.....	2.17	31.76	31.97	....
2.08	31.32	31.42	26.4	2.18	31.795	32.025	26.2
2.09	31.38	31.48	.....	2.19	31.83	32.08	....
2.10	31.42	31.54	26.3	2.20	31.88	32.13	26.2
2.11	31.48	31.60	.....	2.32	31.76	32.02	....

Cooling of calorimeters in twelve minutes, R., 0.12 degree; L., 0.11 degree. Volume of right hand 451 c.c., of left hand 445 c.c. Water equivalent of calorimeters with contents, R., 3,456; L., 3,451. Pulse (sitting) 87. Rectal temperature, 37.65 degrees.

June 12, 1912, he was readmitted to the hospital, complaining of precordial pain, dyspnea, and cough. The right leg pains him more than before. Lips cyanosed. Finger tips bluish. Edema in legs. There is a diffuse wave during systole not prominent in any one region. Limits of cardiac dulness were as follows:

Interspace	Supine Posture Distance in Cm. from Mid-sternal Line		Sitting Posture Distance in Cm. from Mid-sternal Line	
	Right Border	Left Border	Right Border	Left Border
6	9.5	16	12	17.5
5	8.0	15	9.5	15.5
4	6.5	10	6	11.0
3	4.0	7	..	....

Ausculation, with moderate pressure of stethoscope, rough systolic murmur at apex. Pulmonic second accentuated and split. Aortic second, weak. With pressure of stethoscope a soft blowing murmur is heard at apex during diastole. The sounds are reduced in intensity. Free fluid in abdomen.

June 13, 1912, third examination of the hand flow. Hands in bath at 1:58½ p. m.; in calorimeters at 2:09½, and out of calorimeters at 2:25.

TABLE 20. — CALORIMETER MEASUREMENTS IN THIRD EXAMINATION OF ROMAN B.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.09	31.145	31.06	21.4	2.20	31.345	31.47	22.0
2.11	31.13	31.07	.....	2.21	31.37	31.51	....
2.12	31.14	31.095	.....	2.22	31.385	31.545	....
2.13	31.165	31.13	21.8	2.23	31.395	31.59	22.1
2.14	31.18	31.17	.....	2.24	31.405	31.625	....
2.15	31.20	31.225	21.9	2.25	31.415	31.635	....
2.16	31.22	31.26	.....	2.34	31.28	31.51	....
2.17	31.26	31.325	22.0				
2.18	31.29	31.375	.....				
2.19	31.315	31.42	.....				

Cooling of calorimeters in nine minutes, R., 0.135 degree; L., 0.125 degree. Volume of right hand 451 c.c., of left 443 c.c. Rectal temperature 37.3 C. Water equivalent of calorimeters with contents, R., 3,456; L., 3,449.

In a case (Robert T.) diagnosed as pure aortic stenosis with perfect compensation in a man, aged 22 years, the average flow in the hands was at least equal to normal (10.45 grams per 100 c.c. per minute for the right hand and 13.97 grams for the left, with room temperature 20.3 C.). He entered the hospital not for his heart condition, but for surgical treatment.

Robert T., a railroad worker 22 years old, was admitted to the City Hospital Jan. 23, 1913, for surgical tratment (crushed toes on left foot). He had typhoid fourteen years ago; also rheumatism in the neck for several weeks when a child. Denies venereal diseases. For four years after typhoid had shortness of breath and still gets short of breath if he has to hurry up, especially if he changes the

TABLE 21.—CALORIMETRIC MEASUREMENTS IN CASE OF ROBERT T.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Room C.
2.52	31.22	31.13	.....	3.00	31.38	31.42	20.3
2.53	31.19	31.10	.....	3.01	31.42	31.48	....
2.54	31.205	31.12	20.1	3.02	31.47	31.54	20.4
2.55	31.215	31.15	20.1	3.03	31.515	31.59	....
2.56	31.23	31.18	.....	3.04	31.56	31.65	....
2.57	31.27	31.24	20.2	3.05	31.595	31.71	20.4
2.58	31.30	31.29	20.3	3.06	31.64	31.77	....
2.59	31.35	31.36	.....	3.27	31.28	31.41	....

manner of his work, but not when he has become accustomed to a job and can work steadily without spurts. He is well-developed and well-nourished, no cyanosis. Boundaries of cardiac dulness one and a half finger's breadth to left of nipple line, right sternal border, third interspace. A blowing systolic murmur is heard over the entire area, but best in the aortic area where it is exceedingly

loud. From time to time the murmur disappears for one beat, the apex beat becomes weak and the radial pulse vanishes, the murmur corresponding to the next beat being very loud, and the apex beat very strong. The radial sphygmogram is the typical trace of aortic stenosis, with flat top and sloping up-stroke. The heart is slow. The radial pulse shows fair volume, but to appreciate this the artery must be in a particular position as the tension is low and the arm fat. The physical examination reveals nothing abnormal elsewhere. The flow in the hands were measured Jan. 31, 1913. Hands in bath at 2:41½ p. m.; in calorimeters at 2:52½, and out of calorimeters at 3:06. He sat during the whole examination with the injured left foot lying on a stool, the left leg horizontal and the right foot down. (Table 21.)

Cooling of calorimeters in twenty-one minutes, 0.36 degree for R. and L. Volume of right hand 458 c.c., of left 452 c.c. He is mostly right handed, he says. Water equivalent of calorimeters with contents, R., 3,461; L., 3,456. Blood-pressure, left arm, systolic 105 (palpation), 103 (stethoscope), 91 (sound sharply diminished), 87 (sound gone). Rectal temperature 36.6 C.

The last cases to be described are two of mitral stenosis and insufficiency, one with good (Mary S.) and the other with only slightly broken compensation (Frank W.) at the time of the examination. In the first case, a woman, 26 years old, the flow works out at 15.74 grams per 100 c.c. per minute for the right hand and 14.26 grams for the left. Even taking into account the relatively high room temperature (26.7 C.) and the youth of the patient, these flows are, if anything, above the normal.

Fig. 3.—Tracings from Mary S.

When the blood-flow in the hands is not below the normal we are usually justified in assuming that the output of the ventricles is not less than normal. The large flow in this patient agrees well with the obviously exaggerated force of the ventricular stroke, and the absence of venous engorgement, of edema and of cyanosis. It confirms the conclusion that the increased respiratory rate at the time of the examination is a nervous affair not depending on deficient exchange in the lungs. Specimens of polygraph tracings are given in Figure 3. The *a* wave is prominent.

Mrs. Mary S., married woman, aged 26, a Hebrew, was admitted to the City Hospital May 29, 1913, complaining of pain in the chest, weakness and shortness of breath. Seven months before admission she had an attack of acute articular rheumatism and during this attack she began to have pain in her breast. Since then there have been several short periods during which she got short of breath. There seems, however, to be a strong neurotic element in the case, and she does not look particularly ill nor does she show any marked dyspnea. She is fat and well-nourished. No cyanosis, and little, if any, edema of the legs. No venous engorgement, no pulsation in the neck. The thorax is resonant throughout. The breathing everywhere vesicular. The apex beat is in the fifth interspace below the nipple; upper border of cardiac dulness in third interspace, right border, at right sternal margin; left border two finger's breadth out. Auscultation showed the signs of mitral stenosis and insufficiency. The

rather rapid breathing appears to depend largely on nervous excitement. It is certainly not associated with any signs of deficient oxygen intake. The lips are red and she is even more comfortable lying down with her head on a single pillow than sitting up.

The blood-flow in the hands was estimated June 13, 1913. The day was rather warm (external temperature about 80 F). Hands in bath at 2:28 p. m., in calorimeters at 2:40 and out of calorimeters at 2:52. Mouth temperature (two observations) 36.6 C. Pulse (sitting) 84.

TABLE 22.—Calorimetric Measurements in Case of Mary S.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Temp. Room C.
2.39	31.51	31.52	.....	2.47	31.86	31.81	26.7
2.41	31.55	31.57	26.4	2.48	31.90	31.84	....
2.42	31.60	31.60	.....	2.49	31.93	31.87	26.8
2.43	31.65	31.64	.....	2.50	31.97	31.90	....
2.44	31.71	31.68	26.5	2.51	32.01	31.94	....
2.45	31.76	31.73	.....	2.52	32.06	31.99	26.8
2.46	31.80	31.76	.....	3.07	31.89	31.83	....

Cooling of calorimeters in fifteen minutes, R., 0.17 degree; L., 0.16 degree. Volume of right hand 280 c.c., of left 259 c.c. She is right-handed. Blood-pressure, left arm, systolic 114, 95 (second phase), 62 (fourth phase), which was with practically no further fall in the pressure succeeded by the fifth phase (cessation of sound). Water equivalent of calorimeters with contents, R., 3,319; L., 3,302.

The last case is that of Frank W., a man 34 years old, with mitral stenosis and insufficiency with somewhat broken compensation, which was rapidly restored. Three examinations of the hand flow were made. The first on the day of admission, before any treatment had been given, showed a flow of 15.20 grams per 100 c.c. per minute for the right hand and 15.29 grams for the left, with the unusually high room temperature of 30.9 C. At the second examination, three days later, when the patient's clinical condition had improved, the flows were 11.95 grams for the right and 11.55 grams for the left hand, with the lower but still high room temperature of 28.5 C. The third examination, made six days after the second, with a room temperature (30.8 C.) the same as that during the first examination, showed a flow in the right hand of 11.44 grams per 100 c.c. per minute, and a flow in the left of 11.20 grams. The patient was feeling well. The re-establishment of compensation in this case was associated, then, with a diminution in the hand flow of 25 per cent. This diminution in the hand flow coincided with a reduction in the pulse-rate, quieter action of the heart and an improvement of the patient's clinical condition. It must be noted that the loss of compensation when the patient was admitted was not great, that his heart is permanently large and that there are no signs that the myocardium is, as yet, greatly

impaired. The irregularity of the heart noted in the protocol is associated with premature auricular beats (Fig. 4). This condition is not included among the graver cardiac irregularities by those who have specially studied the clinical disorders of the mechanism of the heart beat. Loss of cardiac, or to speak more accurately, of cardiovascular compensation as expressed in an abnormal distribution of the blood, need not be always associated with a diminished flow through the periphery. Doubtless the abnormal distribution of the blood, resulting in engorgement of the venous side of the vascular system and a rise of venous pressure, is harmful, and is going eventually to cripple the machine. Yet it is not difficult to see that for a while the rate of the blood-flow through a part like a hand, far from being diminished, may be increased provided the driving power of the left ventricle, the aortic valves being intact, does not fail. For the rise of venous and therefore of capillary pressure may, up to a certain point, by increasing the caliber of the small vessels, favor the flow of blood. In order that this may result in increased flow through the part it is obvious that the arterial pressure must also be increased so that

Fig. 4.—Tracings from Frank W. The left hand portion of the figure shows simultaneous tracings from the jugular bulb (upper trace) and the radial artery (lower trace). In the right hand portion of the figure simultaneous tracings from the apex (the large elevations) and the radial are given.

a sufficient slope may be maintained. And as a matter of fact, in Frank W., both the systolic and diastolic pressures in the brachial were materially higher at the first than at the second and third examinations. Corroborative evidence for the conclusion that some loss of compensation when the myocardium is not seriously affected is not incompatible for a time with a fully normal hand flow, is found in the observations on Mary S. and P. B., already referred to.

Frank W., an electrician aged 34, was admitted Feb. 9, 1912, to Lakeside Hospital. He says he never had rheumatism. His illness began six weeks before admission with pain all over, especially in the lumbar region and then in the epigastrium. In about a week shortness of breath came on and palpitation of the heart and he became blue in the face. A few days before admission edema was observed in the lower eyelids and the feet. The physical examination showed distended jugular veins with a systolic pulse. Heart: Apex beat in anterior axillary line in fifth interspace. Here there is a systolic impulse and thrill followed by a diastolic impact. A systolic impulse over the conus arteriosus. Left border of cardiac dulness is beyond the anterior axillary line, 18 cm. from the midsternal line, and the right border 9 cm. to right of midsternal line. The

auscultatory signs are those of mitral stenosis and insufficiency. The pulse is irregular and arhythmic. Systolic blood-pressure 145, diastolic 108. Systolic pulsation of the liver. Liver dulness extends to umbilicus in right nipple line. Some edema of lower part of the back. Legs and feet edematous. When dependent, hands and feet are cyanotic. No clubbing of fingers. After a few days' rest the most prominent murmur became the presystolic rumble, heard best at the extreme apex, and indistinct elsewhere. The systolic sound was followed by a short blowing murmur, heard best to right of apex. The size and shape of the heart did not change materially. The edema rapidly disappeared. On March 6 the patient walked out of the hospital feeling well and with good cardiac compensation. The pulse rate which was 160 on admission gradually fell, and varied from 70 to 80 at the time of discharge. The minimum was 58. He broke down again after a time and was admitted to the City Hospital with the same symptoms and physical signs and was discharged improved. He was readmitted June 16, 1913. He worked for three days before he came in but was losing appetite and becoming short of breath. Some edema of the feet and ankles, but not a great deal. Slight cyanosis and dyspnea only on exertion. The point of the nose is red. The boundaries of the cardiac dulness are practically the same as those given in the physical examination at Lakeside Hospital. Pulsation in the neck veins.

The hand flow was measured June 16, 1913, a few hours after his admission and before he had had any drug treatment. The day was very warm. Pulse (sitting) 72, irregular. Hands in bath at 3:11½ p. m.; in calorimeters at 3:22¼, and out of calorimeters at 3:33.

TABLE 23.—Calorimetric Measurements in Case of Frank W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.22	31.49	31.49	.....	3.29	32.09	32.08	....
3.23	31.56	31.55	30.7	3.30	32.18	32.17	....
3.24	31.64	31.64	.....	3.31	32.27	32.255	....
3.25	31.72	31.72	30.8	3.32	32.355	32.34	31.0
3.26	31.82	31.82	.....	3.33	32.44	32.43	....
3.27	31.90	31.90	30.9	3.49	32.37	32.36	....
3.28	31.995	31.99	.....				

Cooling of calorimeters in sixteen minutes, 0.07 degrees.

Volume of right hand in calorimeter 456 c.c., of left hand 452 c.c. Water equivalent of calorimeter and contents, R., 3,460; L., 3,456. Blood-pressure in left brachial 133 (systolic), 103 (change in sound). Another observation 133 (systolic), 133 (change in sound). The pulse was slow and the sound diminished very rapidly to extinction after the change was heard. Rectal temperature 37.55 C.

Second examination June 19, 1913. He says he feels better. He has been receiving digitalis. There is no edema of the ankles, no dyspnea, no distention of the neck veins, no redness of the nose. The day was hot, but not so hot as that of the first examination. Hands in bath at 1:55 p. m.; in calorimeters at 2:10¼, and out of calorimeters at 2:24.

Cooling of calorimeters in twenty-three minutes, R., 0.18 degree; L., 0.16 degree. Radial pulse (sitting) 51. Volume of right hand in calorimeter 450 c.c., of left 439 c.c. Water equivalent of calorimeters with contents, R., 3,455;

L., 3446. Rectal temperature 37.75 C. Blood-pressure left arm, systolic 104, 84 (change in sound); the sound disappeared very soon after this reading. Another observation, systolic 108, 88 (change in sound followed almost at once by its complete disappearance). Pulse (sitting) 60, counted with stethoscope over apex beat. There is still arhythmia. On holding his breath the heart-rate suddenly increased considerably.

TABLE 23.—Calorimetric Measurements on Second Examination of Frank W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.10	31.56	31.47	.....	2.18	32.09	32.02	28.3
2.11	31.61	31.53	.....	2.19	32.165	32.08	....
2.12	31.685	31.60	28.7	2.20	32.215	32.135	28.4
2.13	31.76	31.68	.....	2.21	32.295	32.20	....
2.14	31.83	31.745	28.6	2.22	32.33	32.255	28.4
2.15	31.895	31.82	.....	2.23	32.39	32.305	....
2.16	31.97	31.89	28.5	2.24	32.465	32.36	....
2.17	32.02	31.955	.....	2.47	32.285	32.20	....

Third examination, June 25, 1913. He feels well. Appetite fair, but does not sleep well. Since last examination the pulse-rate has varied between 60 and 72. The respiratory rate has rarely exceeded 20. The temperature has not exceeded 98.4 F. The day was very hot, about the same as the day of the first examination. He says his heart thumps much less than when he first came in although it gives an occasional thump. Hands in bath at 1:53 p. m.; in calorimeters at 2:04¼, and out of calorimeters at 2:19.

TABLE 24.—Calorimetric Measurements on Third Examination of Frank W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.04	31.77	31.73	.....	2.13	32.32	32.26	30.85
2.05	31.78	31.74	.....	2.14	32.39	32.33	....
2.06	31.83	31.80	30.6	2.15	32.44	32.38	....
2.07	31.89	31.85	.....	2.16	32.50	32.44	30.85
2.08	31.975	31.935	30.8	2.17	32.565	32.49	....
2.09	32.04	31.995	.....	2.18	32.62	32.555	30.85
2.10	32.12	32.06	30.85	2.19	32.70	32.63	....
2.11	32.19	32.14	.....	2.35	32.62	32.555	....
2.12	32.26	32.20	.....				

Cooling of calorimeters in sixteen minutes, R., 0.08 degree; L., 0.075 degree. Volume of right hand in calorimeter 443 c.c., of left 432 c.c. Water equivalent of calorimeters with contents, R., 3,449; L., 3,440. Blood-pressure, left arm, systolic 104, 82 (change of sound followed very soon by its disappearance). Another observation. Systolic 109, 86 (change of sound). Pulse (sitting) 60, counted with stethoscope over apex. Respiration (sitting) 18. Rectal temperature 38.0 C.

SUMMARY

1. The smallest flows observed in the series of cases dealt with in this paper have been associated with marked irregularity of the heart, indicating involvement of the mechanism of the heart beat. In some of these cases the cardiac irregularity was associated with valvular lesions, but in those with the very poorest hand flows there was no evidence that the valves were involved.

2. Three cases were diagnosed as auricular fibrillation, all associated with mitral stenosis (and insufficiency). While the flow in all was below the normal it was decidedly greater in one of the patients than in the other two, although he was much the oldest of the three. This corresponded well with his clinical condition, which was good at the time of the examination, better than that of the other two patients. The ventricle in spite of its irregular action was on the whole beating fairly strongly, and was obviously delivering on the average of its beats, a fair amount of blood to the periphery.

3. In a case of mitral stenosis and insufficiency and tricuspid insufficiency, in which the heart showed marked arhythmia in part associated with the respiration (sinus arhythmia) the hand flow was also much below the normal.

4. Abnormally small flows were seen in a number of cases diagnosed as myocarditis with regular action of the heart, but feeble heart sounds not accompanied by murmurs.

5. In some cases diagnosed as myocarditis without valvular lesion, in which a serious clinical condition had previously existed, very fair hand flows, not much inferior to the normal, were found when the clinical condition had markedly improved.

6. In several cases of mitral insufficiency with good compensation and no signs of impairment of the myocardium, the hand flow was found to be quite up to the normal amount. In one case of mitral stenosis and insufficiency the flow appeared to be even somewhat greater than normal as if the big, well-compensated heart were discharging more than the usual quantity of blood.

7. In a case of mitral insufficiency with broken compensation, venous engorgement and edema, but no dyspnea or cyanosis, the hand flow was quite up to normal. In another case with the same lesions where there was little edema, no shortness of breath except on exertion, and none at the time of examination, the flow was also little if at all inferior to the normal flow, and the re-establishment of compensation was associated with an actual moderate diminution in the hand flow.

8. In a case of mitral insufficiency with physical signs of pericardial effusion a flow not much inferior to the normal was found after the patient had been some time in the hospital and had regained compensation, and when the heart dulness had decidedly diminished. When the patient, two days after leaving the hospital, broke down again and

TABLE 25.—DATA CONCERNING

Case	Age	Date	Pulse-Rate	Blood-Pressure	Temperature (C.) of				Volume of Hands in c.c.	
					Room	Art. Blood	Calorimeters		Right	Left
							Right	Left		
Jacob W..	59	5/ 1/11	100	190, (110)	25.0	37.1	29.92	29.93	508	486
					25.1	.....	30.16	.....	...	...
					25.1	.....	30.38	.....	...	...
James M..	60	6/27/12	87	152, 72	23.0	37.15	30.93	30.93	368	356
N. P.	27	5/12/13	70	95	23.8	36.3	31.44	31.33	298	276
Jacob S. ..	44	4/25/11	104	.....	22.2	36.25	29.69	29.62	390	378
					22.6	.....	.....	29.76	...	....
					22.7	.....	.....	29.78	...	....
					22.7	.....	.....	29.83	...	....
T. F. K....	57	5/19/13	120	112, 58	24.0	36.85	31.76	31.75	444	458
Peter B....	59	4/21/11	80	.....	24.5	36.45	30.17	30.14	360	320
					24.3	.....	30.50	.....	...	....
					24.3	.....	30.79	.....	...	....
Peter B...	.....	5/17/11	84	.....	26.6	36.5	30.63	30.43	410†	394†
					26.8	.....	30.80	.....	...	....
					26.8	.....	31.12	.....	...	...
					26.7	.....	31.46	.....	...	....
John T. ..	28	4/ 9/12	100	122	24.4	37.45	31.36	31.44	450	438
					24.3	.....	31.39	.....	...	....
James H. .	63	5/29/13	70	134, 68	23.4	36.1	31.00	30.92	418	396
		6/16/13	57	110, (80)	30.9	37.1	31.69	31.74	408	392
Joseph Z..	16	7/14/11	140	.....	28.1	38.3	30.10	30.10	406	412
					28.2	.....	30.51	.....	...	....
					28.3	.....	30.85	.....	...	....
Mat K....	42	1/24/11	80	170	22.8	36.6	29.72	29.40	440	435
P. B.	31	5/12/11	100	.....	25.5	36.9	30.76	30.68	510	480
					25.8	.....	31.55	.....	...	....
					25.5	.....	32.13	.....	...	....
E. M.	14	1/26/11	116	.....	23.4	38.0	30.14	30.07	255	240
Frank C..	17	12/19/10	116	.....	22.4	37.3	30.19	30.10	275	250
Albert H..	31	4/ 9/12	120	160	24.7	38.6	30.95	30.92	447	450
Albert H..		4/19/12	102	130	22.6	37.2	29.65	29.58	475	505
Albert H..		.....	...	.....	23.8	.....	.....	29.65	...	....
Roman B..	22	5/29/12	96	.....	22.0	37.45	31.41	31.52	454	439
Roman B..		5/31/12	87	.....	26.3	37.15	31.46	31.60	451	445
Roman B..		6/13/12	...	.....	21.8	36.8	31.28	31.36	451	443
Robert T..	22	1/31/13	70	103,(91),87	20.3	36.1	31.44	31.48	458	452
Mary S...	26	6/13/13	84	114	26.7	36.6	31.81	31.78	280	259
Frank W..	34	6/16/13	72	133,(108)	30.9	37.05	32.00	31.99	456	452
Frank W..		6/19/13	60	106, (86)	28.5	37.25	32.04	31.95	450	439
Frank W..		6/25/13	60	106, (84)	30.85	37.5	32.24	32.19	443	432

* Good compensation.

† As his hands were short the marks were put higher up on the wrists than at the previous

‡ Badly broken compensation. The results on Stephen F., Mrs. A. and J. S. W. are sum-

BLOOD-FLOW IN AUTHOR'S CASES

Heat Given Off in Gram-Calories			Blood-Flow in Gm. Per Min.		Flow Per 100 c.c. of Hand Per Min.		Notes
Right	Left	In Mins.	Right	Left	Right	Left	
1,050	801	13	12.50	9.55	2.46	1.96	Myocarditis.
1,225	....	10	19.62	.....	3.86	.....	Left hand in water at 42.9 C.
805	....	7	19.03	.....	3.75	.....	Left hand in water at 11.5 C.
366	270	10	7.32	4.82	1.99	1.35	Senile heart. Arhythmia.
283	216	11	5.88	4.39	1.97	1.59	Auricular fibrillation.
545	238	11	7.69	3.63	1.97	0.96	Auricular fibrillation.
....	170	5	.....	5.82	.....	1.54	Right hand in water at 43.3 C.
....	340	4	.....	14.59	.....	3.86	Right hand in water at 43.3 C.
....	340	5	.....	11.76	.....	3.11	Right hand dried and wrapped.
1,138	1,336	9	27.60	32.34	6.21	7.06	Auricular fibrillation.*
1,180	980	9	23.19	19.17	6.44	5.99	Myocarditis.
1.636	....	10	30.51	.....	8.47	.....	Left hand in water at 42.9 C.
913	....	7	25.62	.....	7.12	.....	Left hand in water at 8 C.
2,156	1,605	10	40.81	29.38	9.95	7.46	
924	....	5	36.03	.....	8.79	.....	Five min. just preceding vasomotor test.
1,643	....	10	33.93	.....	8.28	.....	Left hand in water at 8 C.
1,130	....	9	27.69	.....	6.75	.....	Left hand in water at 43 C.
516	396	10	9.41	7.32	2.09	1.67	Mitral insufficiency.‡
362	.. ..	8	8.29	.....	1.84	.....	Left hand in water at 42.7.
154	119	10	3.35	2.55	0.80	0.64	Mitral stenosis, insufficiency; tricusp. insufficiency; arhythmia.
1,454	1,214	10	29.86	25.16	7.31	6.41	
1,505	1,165	8	25.50	19.75	6.28	4.79	Aortic insufficiency and stenosis.‡
1,402	....	9	22.22	.....	5.47	.....	Left hand in water at 8 C.
1,197	....	..	22.31	.....	5.49	.....	Left hand in water at 43 C.
2,159	1,704	11	31.70	23.90	7.20	5.49	Aortic insufficiency and stenosis.
3,608	3,618	10	65.29	64.63	12.80	13.46	Mitral and tricusp. insufficiency.
2,627	....	11	49.60	.....	9.72	.....	Left hand in water at 8 C.
2,102	.....	9	54.40	.....	10.67	.....	Left hand in water at 43.1 C.
2,988	2,772	13	32.49	29.88	12.74	12.45	Mitral insufficiency.
2,378	2,331	12	30.96	29.97	11.25	11.58	Mitral stenosis and insufficiency.
1,380	1,555	11	18.22	20.45	4.08	4.54	Mitral and tricusp. insufficiency.‡
452	455	7	9.50	9.48	2.00	1.88	
....	472	10	.....	6.94	.....	1.37	Right hand in water at 42.7 C.
3,008	3,970	16	34.58	46.49	7.61	10.59	Mitral insuff. with pericardial effusion.
3,440	4,176	17	39.5	49.18	8.76	11.05	
1,610	2,466	13	24.92	38.74	5.52	8.74	
2.007	2,626	10	47.85	63.15	10.45	13.97	Aortic stenosis.
2,091	1,763	11	44.09	36.94	15.74	14.26	Mitral stenosis and insufficiency.
3.152	3,148	10	69.35	69.11	15.20	15.29	Mitral stenosis and insufficiency .
3,280	3,146	13	53.80	50.73	11.95	11.55	
3,359	3,237	14	50.68	48.38	11.44	11.20	

examination.

marized in a previous paper (Heart, 1911, iii, 84).

returned with some dyspnea, cough and swelling of the legs, the hand flow was found distinctly below its previous value.

9. In two cases of mitral insufficiency with badly broken compensation, with venous engorgement, edema, cyanosis and dyspnea, the hand flow was much below the normal. In one of these cases a striking diminution occurred a few days before death.

10. In a case of apparently pure aortic stenosis with perfect compensation, the hand flow was normal in amount.

11. In a case of aortic stenosis and insufficiency, with mitral insufficiency, while there were no signs of broken compensation, the hand flow was somewhat below the normal.

12. In a case of aortic insufficiency and stenosis, with badly broken compensation (great dyspnea, pulmonary edema), the hand flow was greatly diminished.

While it is obvious that some of the groups of cases are much better represented in the observations than others, as is easily understood, since they had to be collected as chance offered, certain general conclusions which, although of course at present only provisional, are yet entitled to some weight, seem to emerge with sufficient clearness. It is scarcely necessary to say that in some points these conclusions simply confirm what is found by palpation of the radial pulse. But it is by no means true that even the qualitative result of the blood-flow measurement can always be predicted from feeling the pulse.

CONCLUSIONS

1. The hand flow is more apt to be markedly deficient in cases in which there is evidence of serious impairment of the myocardium, or more comprehensively and probably more accurately, of the mechanisms on which the force and rhythm of the heart's action depend, even when valvular lesions are absent, than in cases in which gross valvular lesions exist while the heart's action is strong and orderly. This holds even when in valvular diseases clinical signs of loss of compensation are present. In aortic insufficiency the hand flow appears to be less easily maintained at the normal level and more readily to fall below it when compensation is lost than in mitral insufficiency.

2. Even where there is considerable venous engorgement in cardiac cases the flow in the hands may be little if at all diminished, provided that the myocardium is not impaired. When in a case of broken compensation the flow in the hand remains good the reestablishment of compensation may be associated with a moderate decline.

3. When in a cardiac case with broken compensation the hand flow is normal or not much diminished, the indication is that the myocardium has not as yet suffered serious impairment. A decided diminution in the course of the case may be sigiificant of impending failure of the myocardium.

A STUDY OF THE BLOOD-PRESSURE IN CHILDREN SHOWING ORTHOSTATIC ALBUMINURIA *

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In a previous communication[1] we have reported our findings in an examination of the size, shape and rate of the heart in a series of children showing orthostatic albuminuria. The results of this examination revealed certain abnormalities in cardiac function and in the configuration of the heart, as seen with the fluoroscope. As has been previously pointed out, many children who are the subjects of orthostatic albuminuria reveal clinically signs and symptoms of vasomotor instability which naturally lead one to inquire into the condition of the blood-pressure. We have, therefore, made blood-pressure determinations on a number of these children previously examined in regard to their hearts, and here wish briefly to report our findings.

Systolic and diastolic pressures were determined by the auscultatory method introduced by Korotkow, the stethoscope being held over the brachial artery at the elbow. The instrument used was the one devised by Bendick,[2] the cuff, the same as the one used with the Janeway manometer, being 12 c.c. in width. For the determination of diastolic pressure, that point was taken at which the sound heard over the artery suddenly becomes fainter. This so-called fourth phase has been shown to correspond more accurately to the true diastolic pressure than the point at which all sound disappears.[3] That the readings by the auscultatory method correspond well with those taken by older but more complicated methods has been proved,[4] but owing to its comparatively recent introduction, it has been but little used in determinations on children. A short series of blood-pressure readings taken by the auscultatory method has been quite recently published by E. Mueller;[5] but we have used as controls figures which we ourselves obtained in readings taken on a series of normal healthy boys ranging in ages from 10 to 15 years, whom we were enabled to examine through the kindness of Dr. L. B. Rosenthal, to whom we here wish to express our indebtedness.

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* From the Children's Department of Mount Sinai Hospital Dispensary.
* Submitted for publication August 2, 1913.

1. Bass and Wessler: Heart Size and Heart Function in Children Showing Orthostatic Albuminuria, THE ARCHIVES INT. MED., 1913, xi, 403.
2. Bendick, A. J.: Jour. Am. Med. Assn., 1911, lvi, 1873.
3. Warfield, L. W.: THE ARCHIVES INT. MED., 1912, x, 258.
4. Warfield, L. W.: Interstate Med Jour., 1912, xix, 856; also Goodman, E. H., and Howell, A. A.: Univ. Penn. Med. Bull., 1910-11, xxiii, 469.
5. Mueller, E.: Ztschr. f. Kinderh., 1913, vii, Nos. 3-4.

Owing to the dependence of the albuminuria on the posture of the individual, the blood-pressure readings were taken both in the recumbent and in the upright positions, and as a further test of vasomotor competency readings were taken after a short period of exercise.

The points to be considered then are the following:

1. Do the blood-pressures (systolic, diastolic and pulse-pressures) of children showing orthostatic albuminuria differ in any way from those of normal children?

2. What is the effect of change of posture, recumbent or upright, on systolic, diastolic and pulse-pressure and how do these changes compare with those occurring in the normal child?

3. What is the effect of a short period of exercise (stair-climbing) on the blood-pressures?

4. Is it possible to correlate in any way the findings in the shape, size or rate of the heart before and after exercise with the blood-pressure reactions?

BLOOD-PRESSURE IN THE UPRIGHT POSTURE

Before proceeding to a consideration of our results, it may be well to review briefly the main findings of others in the examination of blood-pressures in normal children. In general, it may be said that both systolic and diastolic pressure increase gradually according to the age of the child. The height and weight of the individual, however, are factors of importance, for in two children of the same age the taller or heavier one will usually be found to have the higher pressure (Wolfensohn-Kriss[6]). Pressure also appears to be affected by the general hygienic surroundings, for Eminet[7] found it higher in children living under good conditions than in those dwelling in poor surroundings. Sex does not appear to influence the pressure in children. All authors are agreed that children show considerable variations in pressure, the same child giving different readings on different days though apparently under identical conditions. Salle[8] found as great a variation as 18 mm. of mercury, but others (Oppenheimer and Bauchwitz[9]) assert that 10 mm. should be considered the normal limit of variation, while Mueller found a daily variation of only 2 to 5 mm. Salle further points out that high readings frequently result from nervousness on the part of the children during examination.

In comparing the results obtained by us in children showing orthostatic albuminuria with those obtained in normal children, we have considered it best to use as controls children of corresponding heights rather

6. Wolfensohn-Kriss, P.: Arch. f. Kinderh., 1910, liii, p. 332.
7. Eminet, P. P.: Arch. f. Kinderh., 1907, xlvi, 328.
8. Salle, V.: Jahrb. f. Kinderh., 1911, lxxiii, 273.
9. Oppenheimer and Bauchwitz: Arch. f. Kinderh., 1905, xlii, 415.

than those of corresponding ages. In Table 1 are tabulated the systolic, diastolic and pulse-pressures of twenty-six children showing orthostatic albuminuria, and in parallel columns the figures for normal children of the same height. The figures for the controls of this series were obtained from the literature and were recorded by means of the palpatory method. This accounts for the fact that the figures for the diastolic pressures in the albuminurics seem abnormally low. As a result of this the pulse-

TABLE 1.—Blood-Pressures in Cases of Orthostatic Albuminuria with Normal Controls for the Corresponding Heights

Orthostatic Albuminurics Blood-Pressure					Normal Controls* Blood-Pressure		
Case No.	Height cm.	Systolic	Diastolic	Pulse-Pressure	Systolic	Diastolic	Pulse-Pressure
1	115	125	65	60	80- 95	70- 90	10-25
2	132	103	85	18	85-115	80-105	5-35
3	121	110	85	25	80-110	75-100	5-35
4	117	80	60	20	80- 95	70- 90	10-25
5	121	112	80	32	80-110	75-100	5-35
6	115	105	60	45	80- 95	70- 90	10-25
7	112	98	55	43	80- 95	70- 90	10-25
8	132	112	65	47	85-115	80-105	5-35
9	126	105	65	40	80-110	75-100	5-35
10	126	92	75	17	80-110	75-100	5-35
11	129	85	70	15	80-110	75-100	5-35
12	131	110	65	45	85-115	80-105	5-35
13	142	103	70	33	80-125	75-115	5-50
14	130	95	70	25	85-115	80-105	5-35
15	130	130	75	55	85-115	80-105	5-35
16	133	120	75	45	85-115	80-105	5-35
17	135	95	70	25	85-115	80-105	5-35
18	131	105	90	15	85-115	80-105	5-35
19	137	110	65	45	85-115	80-105	5-35
20	128	117	87	30	80-110	75-100	5-35
21	157	110	85	35	85-120	85-110	5-35
22	155	107	75	32	85-120	85-110	5-35
23	136	90	75	15	85-115	80-105	5-35
24	140	110	60	50	80-125	75-115	5-50
25	151	120	90	30	85-120	85-110	5-35
26	145	130	95	35	80-125	75-115	5-50

* These figures are from the literature and are obtained by the oscillatory and palpatory methods.

pressures of these children are considerably greater than those of the controls. That this is merely the result of a different method of obtaining the readings will be apparent when Tables 2 and 3 are considered, where the pressures in both the albuminurics and control children were taken by the same (auscultatory) method.

The systolic pressures in eighteen of the twenty-six albuminurics fall within the variations found in health. Eight of the cases, however, show

an increased systolic pressure, varying from 2 to 30 mm. of mercury above the upper limit of the normal figures. A careful reexamination of these eight children, however, failed to show that they differed in any way from the remainder, either in respect to subjective symptoms or in the configuration and size of their hearts. As we pointed out in the previous paper before referred to, we are fairly sure that we have ruled out any cases of nephritis, and therefore do not believe that the increased systolic pressure is due to such disease.

Pulse-pressure varies all the way from 15 to 60, the average being 33. A comparison between pulse-pressure and pulse-rate did not show any evidently constant relationship.

We may, therefore, say that our results of pressure readings taken in the upright posture approximate closely to the figures for normal children. We may also add that though the appearance of some of the children — their loss of vasomotor tone, as evidenced by cold, clammy skin, cyanotic hands and their generally visceroptotic habitus — would lead one to expect a subnormal blood-pressure, in not a single instance did we find this to be the case.

The few figures for similar examinations to be found in the literature correspond with the results above stated. Matthes,[10] who examined twenty-one boys 14 to 17 years of age, all of whom showed "albuminuria of puberty," found normal systolic pressures. Salle,[8] in a very large number of blood-pressure determinations on various types of children, states that the few who were subject to orthostatic albuminuria did not differ in any way from the healthy ones. Finally, Fischl[11] is also inclined to deny any great variation from the normal in the blood-pressures of children showing orthostatic albuminuria, though as he suggests, his readings being a little below the normal, this may be looked on as an evidence of vasomotor instability.

BLOOD-PRESSURE ON CHANGE OF POSITION

In drawing conclusions from the behavior of the blood-pressure consequent on change of position from the recumbent to the upright or vice versa, it should be remembered that different results are obtained when the readings are made immediately after such change, than when some time has been permitted to elapse after the change of position. With this in mind, our readings were not made until an interval of five minutes had elapsed to allow the circulation to adjust itself to the altered static conditions.

In Table 2 are recorded the blood-pressures in both the upright and the recumbent positions. A comparison of the figures shows that the

10. Matthes, M.: Deutsch. Arch. f. klin. Med., 1904-05, lxxxii, 605.
11. Fischl, R.: Arch. f. Kinderh., 1909, lii, 261.

following changes have occurred: On standing up the systolic pressure fell in fifteen cases (average 12.5 mm.); rose in six cases (average 4 mm.); remained unchanged in five. The diastolic pressure under the same conditions fell in eleven cases (average 7 mm.); rose in ten cases (average 8.5 mm.); remained unchanged in five cases. The pulse-pressure fell in twenty-two cases (average 9 mm.); rose in two cases (average 9 mm.), and remained unchanged in two cases.

TABLE 2.—Blood-Pressures in Orthostatic Albuminurics in the Recumbent and Upright Positions

	Systolic			Diastolic			Pulse-Pressure		
Case No.	Lying Down	Standing	Difference	Lying Down	Standing	Difference	Lying Down	Standing	Difference
1	140	125	—15	75	65	—10	65	60	— 5
2	103	103	0	85	85	0	18	18	0
3	105	110	+ 5	75	85	+10	30	25	— 5
4	90	80	—10	65	60	— 5	25	20	— 5
5	110	112	+ 2	85	80	— 5	25	32	+ 7
6	120	105	—15	70	60	—10	50	45	— 5
7	92	98	+ 6	60	55	— 5	32	43	+11
8	115	112	— 3	65	65	0	55	47	— 8
9	103	105	+ 2	60	65	+ 5	43	40	— 3
10	98	92	— 6	70	75	+ 5	28	17	—11
11	98	85	—13	70	70	0	28	15	—13
12	110	110	0	65	65	0	45	45	0
13	98	103	+ 8	58	70	+12	40	33	— 7
14	115	95	—20	85	70	—15	30	25	— 5
15	140	130	—10	75	75	0	65	55	—10
16	120	120	0	80	75	— 5	40	45	+ 5
17	110	95	—15	75	70	— 5	35	25	—10
18	115	105	—10	85	90	+ 5	30	15	—15
19	105	110	+ 5	55	65	+10	50	45	— 5
20	140	117	—23	100	87	—13	40	30	—10
21	130	110	—20	70	85	+15	60	25	—35
22	123	107	—13	80	75	— 5	43	32	—11
23	100	90	—10	77	75	— 2	23	15	— 8
24	112	110	— 2	55	60	+ 5	57	50	— 7
25	120	120	0	82	90	+ 8	38	30	— 8
26	130	130	0	85	95	+10	45	35	—10

It will be seen that in our cases of orthostatic albuminuria there is no constant change in systolic or diastolic pressures on change of position. The pulse-pressure on the other hand with few exceptions was smaller in the upright position.

For a critical consideration of these results it will be necessary to inform ourselves of the data in relation to this subject which are available in the literature. Unfortunately, these disclose no unanimity of opinion, but are rather replete with contradictions. Undoubtedly some of these discrepancies are dependent on the method of blood-pressure determina-

tion used by individual investigators. This applies especially to diastolic pressures, which, when determined by the oscillatory method, as has been heretofore the case, are subject to wide variation and make deductions based on them of doubtful value.

Friedman[12] found that in the erect posture the systolic pressure falls. A similar statement occurs in the reports of Shapiro[13] and Langowoy.[14] With this, Hensen,[15] however, is not in accord, as he frequently failed to note such a change in pressure on standing. Waldvogel[16] considers a drop in systolic pressure on rising as a normal reaction within certain quantitative limits. When such a drop of pressure exceeds 10 mm. of mercury it is considered by him pathologic. Birtch and Inman[17] conclude that in healthy adults not in active training, the systolic pressure is slightly lower in the upright position, the diastolic pressure at the same time is slightly raised with the result that the pulse-pressure is smaller than in the recumbent position. Dietlen[18] regards a slight systolic fall on rising as a normal change, a slight rise, however, not being necessarily pathologic. In twenty-five normal persons he found that on change of posture in 22 per cent. the systolic pressure was unchanged; in 22 per cent. it was higher in the upright position; in 56 per cent. it was lower in the upright position. The diastolic pressure was usually increased, on an average 10.5 mm. when the upright posture was assumed. John,[19] in fifty-two cases, found the pulse-pressure on standing smaller in forty-nine and larger in three cases. Quite recently Barach and Marks[20] have reported a series of cases in which pressure readings were taken on a large number of subjects both in the horizontal and in the upright positions, the experimenters attempting at the same time to eliminate the error caused by muscular exertion in changing from one posture to the other, by placing the subject on a movable platform capable of being tilted either vertically or horizontally. From their findings these authors draw the following conclusions:

When the element of muscular effort has been eliminated change of bodily posture from the erect to the horizontal will cause an increase in the maximum pressure, a decrease in the minimum pressure and an increase in the pulse-pressure. After five minutes in the horizontal posture when the subject is retilted to the erect posture the maximum pressure will diminish, the minimum pressure increase and the pulse-pressure diminish. It will be noted that in both instances the pulse-pressure follows the same trend as the maximum pressure. . . .

12. Friedman: Wien. med. Jahrb., 1882. (Quoted by Dietlen.)
13. Shapiro: Wratsch, 1881. (Quoted by Dietlen.)
14. Langowoy: Deutsch. Arch. f. klin. Med., 1900, lxviii, 268.
15. Hensen: Deutsch. Arch. f. klin. Med., 1900, lxvii, 436.
16. Waldvogel: München. med. Wchnschr., 1908, No. 32.
17. Birtch and Inman: Jour. Am. Med. Assn., 1912, No. 4, 265.
18. Dietlen, H.: Deutsch. Arch. f. klin. Med., 1909, xcvii.
19. John, M.: Deutsch. Arch. f. klin. Med., 1908, xciii.
20. Barach, J. H., and Marks, W. L.: ARCH. INT. MED., 1913, xi, No. 5, 485.

Nearly all the subjects of this series respond in the same way. The most notable exception was in the "poor muscular cases." These showed a tendency to reversal of the pressure curve. From the erect to the horizontal caused in more than half the cases a decrease of the maximum pressure and an increase in the minimum pressure.

We may, with certain restrictions, extract the following conclusions from these data:

1. On change of posture, systolic pressure may rise or fall to a slight degree.

2. In the upright posture diastolic pressure is slightly higher than in the recumbent.

3. Pulse-pressure is smaller in the upright posture.

Using the Korotkow method, we have taken pressure readings of twenty-two healthy boys between the ages of 10 and 14 years. The results of this examination may be seen in Table 3 and may be summarized as follows:

TABLE 3.—INFLUENCE OF CHANGE OF POSTURE ON BLOOD-PRESSURES OF NORMAL CONTROL CHILDREN. READINGS BY THE AUSCULTATORY METHOD

	Systolic			Diastolic			Pulse-Pressure		
Case No.	Lying Down	Standing	Difference	Lying Down	Standing	Difference	Lying Down	Standing	Difference
1	117	120	+ 3	87	80	— 7	30	40	+10
2	105	102	— 3	77	78	+ 1	28	24	— 4
3	112	110	— 2	80	75	— 5	32	35	+ 3
4	100	112	+12	55	55	0	45	57	+12
5	138	140	+ 2	90	90	0	48	50	+ 2
6	135	130	— 5	80	70	—10	55	60	+ 5
7	123	123	0	73	73	0	50	50	0
8	130	120	—10	85	75	—10	45	45	0
9	165	175	+10	115	110	— 5	50	65	+15
10	140	130	—10	120	95	—25	20	35	+15
11	110	112	+ 2	82	90	+ 8	28	22	— 6
12	120	130	+10	60	75	+15	60	55	— 5
13	140	125	—15	75	87	+12	65	38	—27
14	112	120	+ 8	75	77	+ 2	37	43	+ 6
15	115	125	+10	60	70	+10	55	55	0
16	140	135	— 5	50	62	+12	90	73	—17
17	145	145	0	60	75	+15	85	70	—15
18	125	117	— 8	82	90	+ 8	43	27	—16
19	142	145	+ 3	95	85	+10	47	60	+13
20	120	115	— 5	85	90	+ 5	35	25	—10
21	162	142	—20	100	100	0	62	42	—20
22	130	125	— 5	85	80	— 5	45	45	0

In the upright position: Systolic pressure is lower in eleven cases (average 8 mm. Hg); is higher in ten cases (average 6.5 mm. Hg); is unchanged in two cases. Diastolic pressure is lower in eight cases

(average 11 mm. Hg); is higher in eleven cases (average 10 mm. Hg); is unchanged in four cases. Pulse-pressure is smaller in nine cases (average 14 mm. Hg); is larger in eight cases (average 9 mm. Hg); is unchanged in four case.

From these figures it will be seen that in these normal children change of posture resulted in no constant change of the systolic, diastolic or pulse-pressures. Any of these factors may vary in either direction.

If it is assumed for purposes of argument that in orthostatic albuminuria there is some abnormality in the circulation, an assumption that is freely made by most investigators of this condition, one is not unnaturally encouraged to seek in variations in blood-pressure, especially in some alteration in pulse-pressure, some evidence of such an abnormality. Especial impetus was given to this phase of the subject by the work of Erlanger and Hooker.[21] These authors showed in their case of orthostatic albuminuria that the excretion of albumin followed closely a diminution of pulse-pressure resulting from a change of position from the recumbent to the upright. When by various mechanical means such a drop of pulse-pressure was prevented, excretion of albumin failed to take place. This association of fall of pulse-pressure with excretion of albumin led us to hope that in our cases we might find uniformly a decrease of pulse-pressure on change of position from the recumbent to the upright, or at least some evidence of unusual response to postural conditions. Our results as already given, however, do not show any such marked fall of pulse-pressure on change of position, although the figures are somewhat smaller than the controls.

This subject acquires an added interest from its relation to enteroptosis. A majority of our cases show definite stigmata of this condition, probably of congenital origin or disposition. Its significance lies in the abnormality in circulation and blood-pressure, which is supposed to result from an atonic condition of the abdominal wall. Birtch and Inman,[17] in cases of visceroptosis with relaxation of the abdominal wall, concluded that on rising, although the systolic pressure may behave in a normal manner, the diastolic pressure either remains unchanged or drops. They attribute this drop of diastolic pressure directly to a loss of support of the splanchnic circulation due to atonic abdominal musculature.

Such a reaction we have failed to find in our cases. Whatever the effects we may attribute to muscular atony in orthostatic albuminuria, it may be affirmed that a definite change of peripheral systolic, diastolic and pulse-pressure is not one of them. The muscular atony, if it has any effect at all in these cases, operates otherwise than by the production of dynamic changes in the peripheral circulation.

21. Erlanger and Hooker: Johns Hopkins Hosp. Rep., 1904.

In concluding this subject we wish to refer to the statement of Elliott,[22] that a drop of systolic pressure in rising is pathognomonic of cases of orthostatic albuminuria. It is scarcely necessary to say that such a drop of pressure is a normal phenomenon in many cases; and that on the other hand it does not occur with sufficient regularity to invest it with the dignity of an essential symptom.

BLOOD-PRESSURE AFTER EXERCISE

In the search for tests of heart efficiency in both organic and functional circulatory disturbances, the response of the circulatory apparatus to bodily exertion has at various times been used as an index of its capabilities. In orthostatic albuminurics, it is true, there is no question of organic heart disorder in the ordinary sense. We have indeed shown in a previous article,[1] that in many cases the hearts are undersized, abnormal in shape and in some cases have noted what may be regarded as an abnormal response on the part of the heart to increased demands on its energy. Such changes are, however, probably congenital or rather developmental in origin, and their causes lie deeper and are more involved than the ordinary causes of heart disease. It cannot be doubted, however, that functionally the cardiovascular system in these cases is not so efficient as in normal children, in proof of which witness the variety of subjective symptoms of which they so frequently complain, the commonest of which are dyspnea and palpitation occurring even after the slightest bodily exertion.

In attempting to gather some information from the literature on the relationship between blood-pressure and exercise, we are at once confronted with a variety of opinions and numerous contradictory statements. Some, as for example, Stursberg and Schmidt,[23] believe that an examination of the blood-pressure after exercise is of prognostic significance; for they say that an individual, who, after very slight bodily exercise, shows a very large rise in blood-pressure, will be more easily harmed by excessive exercise than one in whom the pressure does not rise so high. This is especially true of those who show marked irritability of their pressure and their pulse-rates. In the same way Kleissel,[24] from experiments on soldiers, concludes that neurotic individuals reveal an increase of blood-pressure and pulse-rates after exercise to a degree not shown by normal persons. As opposed to these views are the conclusions of Fantus and Staehelin,[25] who state that in healthy adults the regulation of the blood-pressure is too complicated for us to draw any conclusions

22. Elliott, A. R.: Interstate Med. Jour., 1911, xviii, 721.
23. Stursberg and Schmidt: München. med. Wchnschr., 1913, No. 4, p. 174.
24. Kleissel, R.: Wien. med. Wchnschr., 1911, No. 28, 1810.
25. Fantus and Staehelin: Ztschr. f. klin. Med., 1910, lxx, 444.

from the behavior of the maximum and minimum pressures after exercise. Masing,[26] as the result of pressure readings on numerous subjects, decides that in general the increase in blood-pressure after work is proportional to the work done; when the work is repeated the increase is not so great. The increase after muscular exercise is in proportion to the mental effort employed, and the latter varies with practice. In young individuals pressure remains high and fairly constant during work, whereas in the aged it drops after having attained its maximum. Finally, Lowsley,[27] after conducting a series of very interesting experiments on athletes, taking systolic and diastolic pressure readings immediately and at intervals after exertion, concludes that the pressure reacts differently depending on the grade of the exercise — whether it be moderate, rapid, vigorous, fatiguing or exhausting. He believes that prolonged exercise which causes an increase in the pulse-rate also causes an increase in systolic and diastolic pressures. The systolic shows the greatest rise; hence there is an increase in the pulse-pressure which may be interpreted to mean that the heart-beats are augmented as well as accelerated. He emphasizes, as an important gauge of the circulation, the time taken for the pulse-rate and blood-pressure to return to normal after exercise. It is also of interest to note in this connection that Lowsley found albuminuria in those cases which showed small pulse-pressures.

Our method of studying the effect of exercise on the blood-pressure was a follows: The pressures were at first determined in the upright position at rest. The children were then made to run up and down three flights of stairs rapidly. The blood-pressure was then immediately taken again, never longer than one-half minute after cessation of the exercise. The need of this haste in making the second reading lies in the well-known observation that the pressure falls very rapidly within a few minutes after the exercise. Readings made after such an interval give quite different results.

Summarizing Table 4, in which we have recorded the results of our blood-pressure determinations in children showing albuminuria we find that the systolic pressure rose in eighteen cases, was unchanged in two and fell in one case. The increase in systolic pressure was as high as 35 mm. Hg. The diastolic pressure fell in thirteen cases, was unchanged in one and rose in seven cases. The greatest fall was 15 mm.; the greatest rise was 15 mm. The pulse-pressure rose in every case after exercise, the rise varying from 10 to 50 mm.

For comparison, we append in Table 5 the blood-pressure of our normal control children taken before and after exercise. When these and

26. Masing, E.: Deutschr. Arch. f. klin. Med., 1902, lxxiv, 253.
27. Lowsley, O. S.: Am. Jour. Physiol., 1910-11, xxvii, 446.

TABLE 4.—Blood-Pressures in Orthostatic Albuminurics Before and After Exercise

Case No.	Systolic			Diastolic			Pulse-Pressure		
	Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference
1	105	100	— 5	65	45	—20	40	55	+15
2	103	105	+ 2	70	60	—10	33	45	+12
3	92	115	+23	75	90	+15	17	35	+18
4	130	130	0	95	90	— 5	35	40	+ 5
5	110	145	+35	85	70	—15	25	75	+50
6	95	113	+18	70	63	— 7	25	50	+25
7	80	100	+20	60	75	+15	20	25	+ 5
8	112	125	+13	80	80	0	32	45	+13
9	105	122	+17	60	68	+ 8	45	54	+ 9
10	85	120	+35	70	85	+15	15	35	+20
11	130	155	+25	75	90	+15	55	65	+10
12	103	106	+ 3	85	65	—20	18	41	+23
13	90	90	0	75	70	— 5	15	20	+ 5
14	120	135	+15	75	70	— 5	45	65	+20
15	110	113	+ 3	85	82	— 3	25	31	+ 6
16	95	125	+30	70	75	+ 5	25	50	+25
17	110	120	+10	65	67	+ 2	45	53	+ 8
18	98	117	+19	55	50	— 5	43	67	+23
19	110	115	+ 5	65	60	— 5	45	55	+10
20	117	125	+ 8	87	85	— 2	30	40	+10
21	120	155	+35	90	85	— 5	30	70	+40

TABLE 5.—Blood-Pressures in Normal Control Children Before and After Exercise

Case No.	Systolic			Diastolic			Pulse-Pressure		
	Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference
1	120	130	+10	80	65	—15	40	65	+25
2	102	135	+33	78	70	— 8	24	65	+41
3	110	127	+17	75	65	—10	35	62	+27
4	112	135	+23	55	65	+10	57	70	+13
5	140	165	+25	90	65	—25	50	100	+50
6	130	160	+30	70	60	—10	60	100	+40
7	123	150	+27	73	55	—18	50	95	+45
8	120	155	+35	75	90	+15	45	65	+20
9	175	175	0	110	95	—15	65	75	+10
10	130	140	+10	95	..	....	35	..	....
11	112	138	+26	90	70	—20	22	68	+46
12	130	150	+20	75	75	0	55	75	+20
13	125	180	+55	87	100	+13	38	80	+42
14	120	160	+40	77	65	—12	43	95	+52
15	125	180	+55	70	70	0	55	110	+55
16	135	195	+60	62	70	+ 8	73	125	+52
17	145	160	+15	75	50	—25	70	110	+40
18	117	160	+43	90	82	— 8	27	78	+51
19	145	180	+35	85	70	—15	60	110	+50
20	115	150	+35	90	100	+10	25	50	+25
21	142	185	+43	100	90	—10	42	95	+53
22	125	170	+45	80	90	+10	45	80	+35

the orthostatic albuminuria cases are compared, the following points may be noted: Both groups react qualitatively in the same manner; the systolic pressures in the orthostatic cases, however, do not increase as much as do those of the normal cases. The diastolic pressures correspond fairly well in the two series. The pulse-pressure after exercise in the cases of orthostatic albuminuria are much smaller than in the controls (as 17:44). This diminution is attributable to the difference in systolic pressures.

SUMMARY

To sum up the result of our investigation we may say that the blood-pressures of children suffering from orthostatic albuminuria differ but little from those of normal children. In spite of the apparent vasomotor insufficiency which many of these children showed, the blood-pressure reactions, both in the upright and recumbent postures and also after exercise, revealed no characteristic anomaly. Nor were we able in any way to correlate the blood-pressure findings with the findings in regard to heart shape and size or pulse-rate. Children with orthostatic albuminuria who showed marked cardiovascular symptoms could not be differentiated by means of blood-pressure tests from the remainder of the group.

These results are disappointing, for the numerous interesting hypotheses concerning the etiology of orthostatic albuminuria would lead one to suppose that the vasomotor system must be in some manner to blame for the condition, especially in view of the results obtained by Erlanger and Hooker. The relationship of lordosis of the lumbar spine to orthostatic albuminuria has also been brought into connection with an abnormal cardiovascular system, since it has been suggested that only those children react to lordosis by an excretion of albumin in whom the vasomotor system is unable to prevent congestion of the kidney. This hypothesis appears plausible, but it cannot be proved or disproved by an examination of the pressure in the peripheral vessels. All that can be said at present is that the blood-pressure in the brachial artery reacts normally, though whether or not this would apply to the blood-pressure in the renal vessels of the same case, we are unable to state.

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EXPERIMENTS TO DEVELOP A MORE WIDELY USEFUL METHOD OF BLOOD-TRANSFUSION *

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In the present discussion a comprehensive review of all methods of transfusing human blood would lead us too far from our immediate subject. It will therefore be expedient to dismiss briefly and with very general consideration those methods of transfusion which involve the direct anastomosis of blood-vessels and not to attempt to estimate their relative merits. For a detailed discussion of the difficulties and limitations of this class of operation the reader is referred to the notable work of Crile published in 1909. Since the introduction of Crile's method, other ingenious devices have been contrived to facilitate the accomplishment of transfusion by an end-to-end junction of the blood-vessels, and there have been numerous accounts of the success of these operations. Less notice, however, has been given of the failures which from time to time have occurred. From a study of the literature, and from the personal communications of those who have had experience with the different ways of performing transfusion by anastomosis, we believe that it is fair to say of such methods that they ought not to be attempted by the general practitioner; that even in the most skilful hands, the presence of some slight adverse condition may seriously interfere with the chances of success; and that in all of these methods there is no satisfactory way of measuring the amount of blood which is actually transfused.

Passing on to those methods of transfusion which depend on the agency of an intermediate receptacle, one finds, in looking over the literature, that such methods were employed many years ago with defibrinated blood, particularly as applied to battle-field surgery. Esmarch, in 1877, in his work on the treatment of the wounded in war, gave a detailed description of the method advocated by him for use in the Prussian army. He believed in using only hydrostatic pressure to carry the blood into the vein; and the illustration which he gives of his contrivance for this purpose bears a very striking resemblance to a modern salvarsan infusion apparatus. Another device of this period was Collin's transfusion apparatus, which consisted of a large funnel and a cylindrical force-pump, communicating by a check-valve with a glass reservoir. From this reservoir, which also served as an air-trap, the blood was led by a tube

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and cannula into the vessel of the recipient. Hasse about the same time employed a screw-piston syringe, and Uterhart a syringe designed to trap air-bubbles. Hürter, another contemporary surgeon, recommended a similar method for arterial transfusion. It is mentioned by Esmarch that injection into an artery of the recipient obviates the danger of over-distending the right heart, and that where a vein is used, not more than 25 gm. of blood a minute should ever be injected.

With all these methods the blood was carefully defibrinated by whipping, and Esmarch recommends two defibrinations and two filtrations to insure against the possibility of injecting coagulum. The question of asepsis was at that time, of course, considered only in the most general way.

About ten years later Esmarch, influenced by the researches of Köhler on the properties of defibrinated blood, came to the conclusion that there is a dissolving action of the fibrin ferment in defibrinated blood on the red blood-cells, and also the possibility of causing coagulative changes in the circulating blood of the recipient, and that therefore "every form of transfusion of blood is to be rejected." A few years later Köhler's work was confirmed by Edelberg and much later by Schultz. In 1900 Esmarch reiterated his condemnation of defibrinated blood and recommended intravenous saline infusion for every indication that formerly demanded transfusion. Fuld, in 1903, and Morawitz in 1905, showed that the harmful substances in defibrinated blood was changed to an apparently harmless modification if filtration from the coagula was conducted without pressure, and if the blood was kept for a short time after defibrination before being injected into the circulation.

Those who have more recently experimented with the use of homologous defibrinated blood for intravenous transfusion vary in their estimate of the value of the procedure as a therapeutic method. Morawitz, in a later communication, says that there is great danger in infusing defibrinated blood into the circulation unless ample time has been allowed for the completion of all changes which may take place in the coagulative factors. The experiments of Moldovan indicate that thirty-five minutes after defibrination is the time-limit of safety. Although Curtis and David have given intravenous injections of freshly defibrinated blood in dogs in four experiments and found it to have been safely utilized by the recipient animal, these authors are not led to advocate the method for human transfusion. Hürter asserts his belief, based on clinical results in thirty-five transfusions for pernicious anemia, that the use of fresh unaltered blood is much better than the use of defibrinated blood, especially in the aplastic type of this disease. The investigations of Pike, Guthrie and Stewart on the resuscitation of the blood, indicate that the preservation of defibrinated blood for twenty-four hours impairs the

physiological functioning of the erythrocytes, and they express the belief that blood, when preserved outside the circulation, soon undergoes changes which affect its nutritive as well as its bactericidal properties. The experiments of Genou in 1901 apparently indicated that plasma had little or no bacteriolytic action *in vitro* on a variety of organisms which were destroyed by serum. This supported Metchnikoff's theory that complement is derived from the leukocytes and liberated by changes induced in them during the process of coagulation. Addis, however, has since shown that Genou did not directly compare plasma with serum, but serum from cell-free plasma with serum from blood, and concludes from his experiments with "paraffin plasma" which he obtained by a very careful technic, that complement is not derived from injured leukocytes, that there is as much complement in plasma as in serum, that it is probably present in the circulating plasma of the blood and is not a product of coagulation.

Stevens and Lee, in 1884, in the course of perfusion experiments with defibrinated blood on the frog and terrapin, demonstrated the presence of an active vasoconstricting substance in defibrinated blood which was apparently due to some product of the coagulative process. The experiments of Brodie were, however, the first to indicate that there were distinctly different vasomotor agents in plasma and in serum, the main result of his investigations being the discovery of a vasodilator substance in blood-serum acting centrally on the vasomotor system through the pulmonary branches of the vagus, which this author determined to be a protein of the albumin class, coagulable by boiling and produced during the process of clotting by some action of the corpuscles. Sollmann found that serum produces a direct vasodilator effect on the isolated kidney limited to the efferent vessels, and O'Connor determined that the vasoconstricting effect of serum was due, not to its epinephrin content, but to some substance liberated during coagulation. O'Connor's observations were later confirmed by Falta and Fleming, and the existence of such a substance was inferred by Stewart and Harvey from their finding that the serum from a patient with Addison's disease, whose adrenal remains after death yielded no suprarenin, produced as great a constrictor effect on the vessels of an isolated rabbit kidney as did normal serum.

Stewart and Harvey followed up this observation with a series of perfusion experiments showing the effects of human, dog, rabbit and sheep serum and plasma on the isolated renal vessels of the dog and rabbit, on the peripheral vessels of the rabbit and frog, and on the coronary arteries of the isolated rabbit heart, and came to the conclusion that there is: (a) a vasodilator substance in plasma and in serum which is specific for the vessels of the kidney, acting directly on the muscle coats of the arteries, which is a protein of the albumin class and is precipitated

by boiling and by alcohol; (b) a vasoconstrictor substance in serum, liberated by the process of clotting of the blood, which acts on the renal vessels and also on the vessels of the limb, which is not a protein, is soluble in alcohol and resists boiling.

If these conclusions be accepted as the vasomotor effects of plasma or undefibrinated blood and of serum or defibrinated blood, it is evident that the action of the latter must be a complex resultant of opposed forces.

That a deleterious effect is produced by the presence in blood intended for transfusion of substances having such a complicated action on the vasomotor system, would be difficult to prove in any given case. But, generally speaking, it is desirable beyond peradventure that blood for transfusion should be without any alteration of normal physiological function, except where some special therapeutic effect is sought, as from specifically immunized blood. Apart from the dangers of insufficient defibrination, the chances of bacterial contamination, and the other objections just mentioned, the use of defibrinated blood seems particularly inadequate from a physiological standpoint in those cases (purpura, hemophilia, etc.) in which the potential clotting elements of the patient's blood are presumably lacking or at fault.

The transfer of fresh blood from one human being to another through the agency of an intermediate receptacle seems to have been first practiced by von Ziemssen over twenty years ago. The method described by this author required one operator and three assistants. The arm of the donor was congested by a bandage and a prominent vein at the bend of the elbow was punctured without skin incision by means of a hollow cylindrical needle and the blood was withdrawn into a 25 c.c. piston syringe. While this syringe was filling another needle was likewise introduced into the recipient's vein. The ligature was then removed from the recipient's arm and the first syringe, as soon as filled, was quickly carried over and attached to the needle in the recipient's vein and the blood slowly injected. Meanwhile a second syringe was attached to the donor's needle as soon as disconnected from the first syringe, and the same procedure repeated. A third syringe followed in the same way, the first one being meanwhile carefully washed out by an assistant. Ziemssen reported that the transfer of from 250 to 300 c.c. of blood in this manner took not longer than fifteen to twenty minutes. In his first series of seven cases he stated that he observed chills and elevations of temperature in three cases and that in one of these instances he had trouble with a clot in the recipient's needle which had to be removed. He, however, considered the method less liable to the risk of causing dangerous coagulative changes in the circulating blood than transfusion by end-to-end anastomosis or the use of defibrinated blood.

A method was recommended by Moritz in 1911 which did not materially differ from Ziemssen's, except that the needles were fitted with stop-cocks and connected with the syringe by means of an intermediate tube of glass and rubber also provided with stop-cocks. Immediately after each withdrawal or injection of blood, sterile normal salt solution was injected through the needles and the stop-cocks were closed. Strips of adhesive plaster were used to minimize as far as possible the movement of the needles while within the veins. It is mentioned by Moritz that the needles are of such fine caliber that no clots of any size could possibly be injected into the circulation. Hürter recommends Moritz's method and claims to have had success with it although he refers to it as involving a delicate technic.

More recently Lindeman has advocated a method which he has practiced successfully on children and adults in a considerable number of cases. His method differs from that of Ziemssen and of Moritz in that he has devised a special set of invaginated cylindrical cannulas, and that a dozen or more syringes of 20 c.c. capacity are employed in rapid succession to convey the blood from one cannula to the other. An improvement over the Ziemssen and Moritz technics is the avoidance of traumatizing the intima of the veins by the many abrading movements within the blood-vessel of a sharp-pointed instrument, incidental to the frequent connection and disconnection of the syringes. This feature is minimized by Lindeman in that the sharp innermost cannula of his set is withdrawn from the vein as soon as it has done its work of penetration. It should also be mentioned that all cannulas receive an internal coating of liquid paraffin before use.

As no special measures to delay or prevent clotting of the blood while in the receptacle are employed in this class of operation, success and safety necessarily depend on celerity of action in conveying the blood from the vessel of the donor to that of the recipient. Prompt and repeated washing out of the cannulas with normal salt solution is also imperative. Each syringeful of blood involves one interruption of flow, two connections to blood-vessels and two disconnections, which subjects the punctured vein-wall to a considerable amount of manipulation during the course of the transfusion. Where much blood is to be transfused by this method many syringes are required, and this makes the outlay for apparatus a matter for consideration in judging of the general usefulness of the procedure. To keep a dozen or more syringes in good working order with strict asepsis, and to have the intelligent, prompt and coordinated action of at least three operators, renders this type of operation impossible for emergency use except in a hospital, and takes it out of the hands of the general practitioner. We believe, however, that this method in its simplest application, as reported by Cooley and Vaughan, should prove

a valuable resource in emergencies, where only 10 to 20 c.c. of blood are required, and an ordinary syringe with needle is the most convenient instrument at hand.

It is evident to anyone who has given it consideration that a large field of usefulness would be open to the operation of blood-transfusion if it could be performed safely, quickly and surely by anyone possessing ordinary surgical skill, and, if possible, without expert assistance.

It occurred to one of us that such a practicable method might be evolved if a satisfactory apparatus could be devised to withdraw a considerable quantity of blood at one time from a vessel of the donor and inject it into a vessel of the recipient without risk of clotting; and more particularly from a study of the recent investigations of Howell, of Duke and of Whipple on the nature and significance of the factors concerned in blood-coagulation, it seemed that there were two alternative lines of experimentation which held out some promise of overcoming the danger of clotting in blood-transfusion. These alternatives are:

(*a*) The employment of an intermediate system, providing no point of contact with any moistenable surface, and at the same time minimizing as far as possible the exposure of broken tissue surface to the blood-stream; (*b*) the employment of a sufficient amount of some physiologic agent (antithrombin), to restrain or offset the initiative factors of coagulation during the time of the conveyance of the blood through a foreign system, such as glass and metal.

The investigation of the possibilities of the second of these alternatives is already under way and will form the subject of a later communication.

It is, however, with the development of the first of these procedures that the present paper has to do; and we may say at once that this has resulted in a method of drawing blood from the donor's blood-vessel directly into a paraffin receptacle, carrying the blood to the recipient, and injecting it into the recipient's circulation in precisely the same way in which it was obtained from the donor. Excepting the air-contact of its upper surface while in the receptacle, the blood does not touch anything but paraffin during its passage. The paraffin receptacle consists of a thin film of hard paraffin, lining a firm supporting structure. The latter comprises a tubulated glass cylinder, closed at the lower end by an asbestos stopper, through which passes a metal cannula. The upper end of the cylinder passes directly into an aspirating tube containing an air-filter and terminating in a mouth-piece.

In considering the work which has already been done with paraffin-coated apparatus, we have been especially impressed with the reports of Curtis and David, and of Risley and Irving. From the findings of these investigators it seemed wise to plan some preliminary experiments to ascertain the essential requirements of a conveying system with a protective lining.

The materials which appear to have served best as anticoagulative coating agents in former experimental work[1] are the paraffins, ordinary commercial petrolatum, the neutral saponifiable oils and stearic acid. The latter seemed to possess no peculiar advantage and was rejected by us on theoretic grounds, because of the possible hemolytic effect[2] which is known to be a characteristic of some of the unsaturated fatty acids. The trial mixtures were, therefore, confined to ingredients of the first three classes. Olive oil and the expressed oil of almonds were chosen from the neutral saponifiable oils, and, when combined in proper proportions with paraffin and petrolatum, formed fairly satisfactory mixtures. The vegetable oils were, however, finally abandoned on account of their tendency to favor the growth of mold.

In judging the suitability of the paraffin mixtures, the physical qualities considered were:

1. Macroscopic smoothness and uniformity of surface, and microscopic fineness and uniformity of reticulation.

2. Cohesiveness and adhesiveness to glass, silver and asbestos when congealed.

3. Greasiness of surface, as judged by repulsion and globulation of watery fluids.

As a final test, glass tubes of 2 mm. internal diameter, coated with the mixture, were tested by aspirating a short column of blood directly from the vein of an animal, and the relative clotting-time of this blood-column was observed and compared with that in a similar tube without coating.

The combination finally adopted as the best of twenty-four mixtures tested was:

Grübper's filtered paraffin, melting point 60 to 62 C. (140 to 143.6 F.), 56 parts by weight, and pure white petrolatum, 44 parts by weight. This mixture has a melting point of 49 to 50 C. (120.2 to 122 F.).

Experiments to develop the best form of cannula and blood-receptacle were carried out as indicated in the reports of Experiments 1 to 4, inclusive. Several glass cylinders having a piston or plunger discharge were abandoned, as this type of apparatus was found difficult of control for slow delivery, uncertain in action, required the use of a third hand in effecting the transfer, and was not nearly so delicate as the simple pneumatic discharge assisted by gravity, which was afterward adopted.

Experiments with needles and cannulas for introduction into the vein led to many changes before a satisfactory method was evolved. It

1. Bernheim, B. M.: Jour. Am. Med. Assn., 1912, lviii, 1007. Bordet and Genou: Ann. de l'Inst. Past., 1903, p. 822. Brewer and Legget: Surg., Gynec. and Obstet., 1909, ix, 293. Vincent, B.: Am. Jour. Dis. Child., 1911, i, 376.

2. Adler, H. M.: The Archives Int. Med., 1913, xi, 187. Hopkins, A. H.: The Archives Int. Med., 1913, xi, 300.

was found impossible to coat with paraffin a cylindrical needle and flexible connecting tube in conjunction with a glass container, so as to preserve an intact coating throughout the entire system, and at the same time provide a sufficiently wide channel for effectual aspiration and delivery. The wax mixture was, therefore, in the next experiments, used for coating the glass containers only, and oil or liquid paraffin was resorted to as a coating for the needles and tubing. This makeshift worked with moderate satisfaction on the experimental animal, but is open to at least a theoretic objection on account of the considerable amount of liquid oil which may enter the circulation, and the practical objection that with a flexible connection the whole aspirating apparatus cannot be held and

Fig. 1.—Longitudinal section of cannula seated in asbestos stopper of pipet.

the cannula directed into the vein with one hand, while the other hand of the operator is left free to fix the wall of the vein. At this stage of our investigation it became evident that it would be advantageous to devise a special cannula rigidly connected with a glass cylinder, forming a pipet. The construction of this instrument was based on several important principles which a diagram will elucidate (Fig. 1).

The point of the instrument is conical in shape and is designed to stretch apart the tissues penetrated, while effecting the least possible injury. The distal opening of the cannula is placed laterally and the edges of this opening are smoothly rounded. The thickening or shoulder

just back of the opening serves as a stop and prevents possible leakage when the cannula is pushed into the vein.

It will be seen, by reference to Figure 1 that the cylindrical part of the lumen extends for only a fraction of an inch, and then immediately widens. This enlargement, though appearing as a very gradual taper, provides an increase in the circumference proportionate to the increase of the radius, and an increase in the area of the cross-section proportionate to the squares of the radii; so that at the point *B*, which has a diameter double that of point *A*, the circumference of a contained column of fluid is only doubled, but its volume is increased four times. This means that at *B* the degree of lateral contact of the column is diminished one-half in relation to the sectional area of the column at that point.

The wall of a tube of small diameter, which can be wet by a contained fluid, necessarily determines a certain amount of lateral friction on a

Fig. 2.—Distal end of cannula showing position in vein. Shoulder just back of opening prevents leakage from blood vessel.

moving column of that fluid, the peripheral layer of the column adhering so closely to the wall of the tube as to be practically motionless. It is obvious that a paraffin coating on the wall of such a tube materially lessens this peripheral friction. That friction is also lessened by expanding the caliber of the cannula and reducing its length to a minimum, may be readily deduced from the law of Poiseuille for determining the outflow of fluid from capillary tubes. This law may be expressed by the equation:

$$Q = \frac{D^4 H}{L}$$

That is to say, the quantity, *Q*, which is discharged in a unit of time is directly proportional to the fourth power of the diameter, *D*, of the

tube, and to the height of the pressure, *H*, and indirectly proportional to the length of the tube, *L*. It may furthermore be reasonably assumed, and there is experimental evidence to support the assumption,[3] that diminished friction of blood in a foreign system, is associated with a diminished tendency to coagulation.

The important feature of the short attachment of the cannula to the neck of the pipet is contrived by means of an air-tight asbestos stopper, enclosing the proximal end of the cannula and making the latter an arm

Fig. 3.—Pipet with cannula in position for insertion in vein.

of the pipet, the two members together forming virtually a rigid one-piece apparatus (Fig. 3).

METHOD OF PREPARATION AND USE OF APPARATUS

The process of coating the inside of the apparatus with paraffin requires a careful technic to be successful. The pipet must be thoroughly cleaned and free from moisture, and two coats are applied. The first

3. Hürthle, K.: Archiv. f. d. ges. Physiol., 1900, lxxxii, 436-438.

coating is done at 68 to 71 C. (154.4 to 159.8 F.) in a bath containing a quantity of the paraffin mixture sufficient to allow the cylinder to be immersed for its entire length and to a depth of at least half its diameter. It is then rotated in the melted wax until uniformly heated. Air-bubbles must be avoided in the removal of the cylinder from the bath, and the coating must take place under sterile precautions. When the first coating is thoroughly hardened a sterile aspirating tube is attached, and the sterile asbestos stopper and cannula are snugly inserted (Fig. 4).

The second coating is applied by aspirating the hot paraffin mixture from the bath, at a temperature of 60 to 61 C. (140 to 141.8 F.) through the cannula into the cylinder. When the inflowing paraffin has reached a level of about 1 cm. above the neck of the pipet, it is immediately

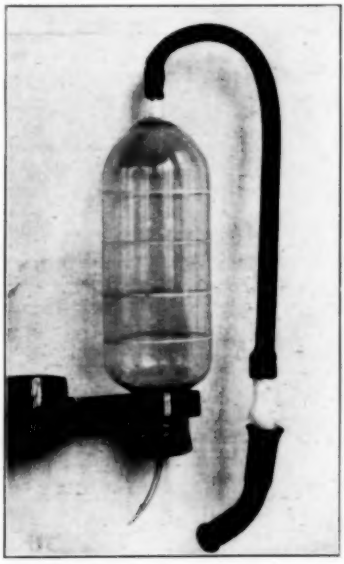

Fig. 4.—Pipet and cannula with aspirating tube and mouth-piece attached.

expelled. The cannula is then lifted from beneath the surface of the bath and its lumen quickly cleared by gentle blowing through the mouth-piece, care being taken to avoid any back suction which would result in air-bubbles. The cannula is finally protected by covering with a piece of sterile-glass tubing held in place by a strip of adhesive plaster.

In warm weather the apparatus should be prepared at least one hour in advance of use so as to allow the paraffin to harden thoroughly. If a sharp cannula is used, attention must be given not to damage the point when coating the apparatus, and in every case its lumen must be smooth and clean before coating.

It should be stated here that both sharp and blunt-pointed cannulas have been used. The use of the former constitutes the simpler method of penetrating the vein when the size of the blood-vessel admits of free manipulation, but a fine probe point is to be preferred in most cases, especially if the vein is small and the danger of wounding or penetrating the opposite wall is, therefore, increased.

METHOD OF TRANSFUSION

The method of transfusing with the blunt-pointed cannula is as follows:

Instruments.—Knife, scissors, thumb forceps, fixation forceps, one or two mosquito clamps, several self-retaining stylets of different sizes (Fig. 5), sutures and needles for closing the skin wound.

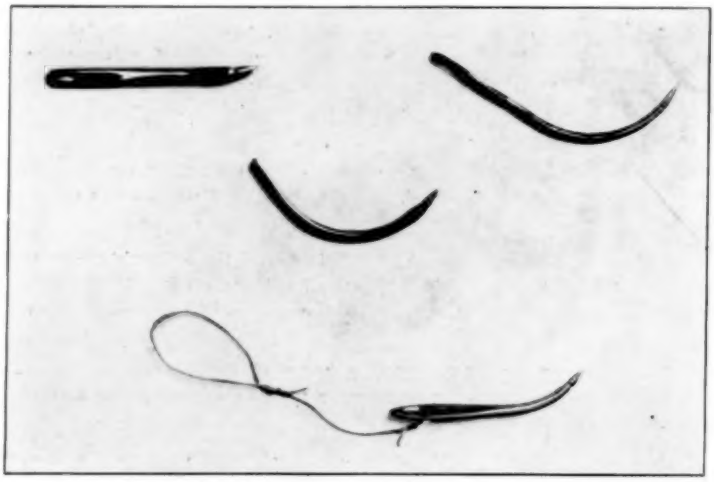

Fig. 5.—Self-retaining stylets used to puncture blood-vessel.

Apparatus.—Several prepared pipets having cannulas of the size likely to be needed for the case at hand, two obturating sleeves with clamps attached; a small tube of sterile liquid paraffin and some sterile petrolatum; a sterile aspirating tube; a cotton air-filter, and a mouth-piece.

Operation.—The donating and recipient veins are exposed under local anesthesia in the usual manner through incisions about 4 cm. in length, and the fascial sheath is cleared away so that a firm hold of the vein-wall can be secured. A pipet with a cannula suited to the size of the recipient vein is chosen, the aspirating tube with mouth-piece is attached and an obturating sleeve, with clamp attached, is dipped into sterile liquid

paraffin and slipped over the cannula. The action of the sleeve is tested to make sure that it will slip easily backward and forward and it is then retracted to a position just proximal to the shoulder of the cannula. Suitable stylets are selected, dipped in sterile petrolatum, and inserted through the walls of both veins. The direction of penetration should be with the current in the recipient vein and against the current in the donating vein. The operator, having taken the mouth-piece and holding the pipet in his right hand, fixes the wall of the donating vein with a forceps in his left hand immediately beyond the point where the stylet has just been introduced, and exerts slight traction upward. The stylet is then quickly removed, by means of its attached loop, with a finger of the right hand, the traction on the vein controlling the outflow of blood; and the cannula is then pushed through the small hole which has been punctured by the stylet. The arm of the donor is now constricted above, and the blood is drawn into the pipet by aspiration. When enough blood has been obtained the cannula is withdrawn from the vein with one hand, while with the other hand the obturating sleeve is pushed to its distal position covering the mouth of the cannula a moment after it emerges from the vein. A little blood is purposely allowed to flow from the cannula at this juncture to remove any thromboplastic substance which may have been collected from the broken surface of the vessel-wall at the moment of withdrawal. The duties of an assistant, who may be the donor himself, are to remove the constriction of the arm when the blood has been obtained and to press a sterile gauze compress over the wound until it is ready for suture. Introduction of the blood into the vein of the recipient is accomplished in precisely the same way as just described for its withdrawal, except that the fourth or fifth finger of the right hand of the operator is used to retract the obturating sleeve at the moment of entering the vein.

The capacity of the pipet which has been found most useful is about 225 c.c. It is probably inadvisable to take more than 200 c.c. of blood at one time. A second pipet can be used for a second transfusion if desirable. Not more than twelve minutes should elapse in making a single transfusion with safety. One hundred and fifty c.c. should be obtained in from two to five minutes, depending on the abundance of blood-flow in the donor's arm; and this should be injected in from four to six minutes. There is probably no danger of overdistending the right auricle if delivery is effected no faster than 50 c.c. per minute for an adult, and 20 to 25 c.c. per minute for a child.

In conclusion we present, in chronologic order and as briefly as the details will permit, a report of our experiments in transfusing animals with this apparatus, together with our clinical application of the method in three cases.

EXPERIMENTAL AND CLINICAL REPORTS

EXPERIMENT 1.—Feb. 12, 1913: Dog 1, male, 5.81 kg. Ether anesthesia. Femoral and external jugular veins exposed.

Apparatus: glass cylinders with asbestos-packed piston plungers; two openings at opposite ends of cylinder, one for aspiration and one for delivery. Cylinders previously coated with the plunger in position for delivery. Paraffin mixture 2. Delivery tube of rubber, 5 cm. in length, coupling the glass cylinder to an ordinary hollow needle of medium size (1.16 mm. external diameter). Delivery tube and needle not coated.

Aspiration of blood accomplished by suction with rubber bulb connected by tubing to proximal opening of cylinder provided for the purpose. When cylinder was filled with blood this opening was shut off and delivery effected by advancing the plunger. The tubing and needle were tried at first dry and then with an internal coating of oil. The blood clotted promptly in the tube and needle in the first instance, and less promptly in the tube and needle which had received the coating of oil. A much more satisfactory delivery was effected by the use of a tapered cannula with oil coating. The blood remained fluid in the paraffin-lined glass cylinders from nine to eleven minutes, the temperature of the room being about 20 C. (68 F.). The action of the plunger was found to be uncertain and difficult to control. The dog was killed at the end of the experiment.

EXPERIMENT 2.—Feb. 14, 1913: Dog 2, female, 6.34 kg. Ether anesthesia. Both femoral and external jugular veins exposed.

Apparatus: glass cylinder, about 80 c.c. capacity, previously coated with paraffin mixture No. 7, having two openings at opposite ends, one for pneumatic aspiration and expulsion of the blood, and the other for connection as in last experiment. A specially modified tapered cannula and large size (1.62 mm. external diameter) cylindrical needles were employed; cannula, needles and connecting tubes were coated with oil.

First trial (tapered cannula): 60 c.c. of blood taken from jugular and without difficulty discharged into femoral vein. The small amount of blood remaining in cylinder clotted in twelve minutes thirty seconds.

Second trial (cylindrical needle): transfusion not effected owing to clotting in needle.

Third trial (tapered cannula): 40 c.c. taken from femoral and without difficulty discharged into jugular. The small amount of blood reserved in cylinder clotted in approximately fifteen minutes. The dog was killed at the end of the experiment and the veins were dissected out and opened. No evidence of clotting was in the veins.

EXPERIMENT 3.—Feb. 15, 1913: Dog 3, male, 9.9 kg. Ether anesthesia. Aseptic precautions. Right femoral and right jugular veins exposed.

Apparatus: glass cylinder communicating directly through stopper with a specially curved and tapered cannula. The entire apparatus provided with an intact coating of paraffin mixture 9. The result of the preliminary test of the coagulation time of the dog's blood (Biffi-Brooks method) was that at 37.5 C. (99.5 F.) at the end of two minutes there was a slight fibrin formation; at two minutes forty seconds a slight fibrin formation; at four minutes a complete clot. About 48 c.c. of blood were aspirated from the jugular vein by means of a rubber bulb, an aspirating tube was clamped, the cannula withdrawn and the hole in the vein clamped with mosquito clamp and subsequently tied with fine catgut. There was considerable dripping of blood from the cannula which obscured the field of operation and required sponging with salt solution. The cannula was introduced into the exposed femoral vein in the same manner and about 45 c.c. of blood was discharged and the puncture hole tied off as before. The time of entrance of the cannula into the first vein to the withdrawal from the second

vein was a little more than four minutes. Most of the blood reserved in the pipet was allowed to run out six minutes five seconds after withdrawal from the first vein, and a four-loop preparation of this was taken and transferred to the chamber of a Biffi-Brooks coagulometer with observation as follows:

Temp. 35 C. (95 F.), forty seconds; no clotting.

Temp. 34.6 C. (94.2 F.), one minute forty seconds; no clotting.

Temp. 33.2 C. (91.7 F.), four minutes thirty-five seconds; fairly firm clot.

The skin wounds were closed, collodion dressing applied and the dog allowed to come from under the anesthetic. The small amount of blood reserved in the pipet was examined at thirty-five minutes after withdrawal from the vein. That portion remaining in the cannula and in the cylinder adjacent to it was found clotted, but the larger portion which had flowed back in the cylinder as it lay in the horizontal position was still fluid. A loop of this was removed to the coagulometer and found to dissipate completely when plunged into water. The dog appeared perfectly normal after the operation and showed no subsequent ill-effects.

Clinical Trial, Case 1.—Feb. 16, 1913: E. B., a girl aged 7½, was admitted to the hospital Jan. 24, 1913, with scarlet fever, in the eighth day of her illness. Temperature 103 F., pulse 138, respiration 24; heart, lungs, abdominal organs and urine were negative on admission. The patient appeared to be making a good recovery until February 6, when she had a chill and a sudden rise of temperature to 105.8 F., and several days later developed signs of a nephritis. By February 12 she had a fully developed purpuric rash with scant bloody urine and joint pains. February 14 an uncontrollable oozing hemorrhage started from the nose, the condition of the patient became rapidly worse and a systolic heart-murmur developed. Horse-serum, 10 c.c., was given subcutaneously. February 15 the epistaxis continued; there was evidence of cardiac dilatation on percussion; vomiting of blood recurred at intervals; the hemorrhagic rash was very marked and widely distributed. Horse-serum plugs were placed in the nostrils and 20 c.c. horse-serum given subcutaneously. February 16 the patient vomited bloody fluid continually, retained no food or medication by mouth, the temperature was 98.4 F., pulse 160 and hardly perceptible at the wrist, respiration 26; a tarry stool was passed at 4 p. m.; the condition was evidently moribund. The father was summoned and offered to serve as donor for a transfusion. Apparatus similar to that in Experiment 3 was used, and 65 c.c. of blood was removed from the donor's median basilic vein and injected into the median cephalic vein of the patient. The transfer took place in approximately three and one-half minutes. No difficulty of any kind was experienced except for the dripping of blood from the cannula at the moment of entering the recipient vein, which required sponging. The small amount of blood remaining in the pipet did not clot until twenty-one minutes after withdrawal from the vein. The patient's pulse and mental condition seemed slightly better shortly after the transfusion, but death occurred early on the morning of the following day.

A condensed report of the macroscopic findings at the autopsy, performed by Dr. George P. Biggs fourteen hours after death, follows: Heart: distinct dilatation of the left ventricle, petechial hemorrhages of the endocardium and hemorrhagic areas in the papillary muscles on cross-section. Kidneys: considerably enlarged, capsules not adherent, surface smooth, pyramids and cortex both greatly swollen, cortex light in color and markings indistinct. Suprarenals: rather large, left containing a small area of softening in the upper portion, the right a small area of softening in the lower portion; no definite hemorrhages. Ulcerative lesion of the left tonsil and base of the tongue with erosion of blood-vessels. Multiple hemorrhagic areas of the lungs and spleen. Petechial areas widely distributed over skin, mucous membranes and serous membranes.

Experiment 4.—March 11, 1913: Dog 3 (the dog used in Experiment 3) Ether anesthesia. Right jugular and right femoral veins exposed.

Apparatus: A new pipet, similar to that used in last experiment, but graduated and arranged for mouth aspiration with sterile cotton air-filter. A sharp tapered cannula was used as in Experiment 3, but was cemented into an asbestos stopper. This was made by winding very thin asbestos tape, 1 inch wide, about the shank of the cannula as a core. The fiber of the asbestos was bound centrally and marginally by impregnation with a solution of sodium silicate, and medium size asbestos twine was used as an outer binding. The apparatus was coated with paraffin mixture 10.

One hundred c.c. of blood were transfused from the jugular vein to the femoral. The trnsfer was easily effected except for dripping blood when entering the second vein. The time of operation was approximately six minutes. The same amount of blood was removed from the femoral and partially discharged into the jugular; some difficulty was experienced in entering the vein due to the sharp cannula, insufficient exposure of the blood-vessel and obscuring of the field by dripping blood. The dog was killed at the end of the experiment. The same veins were used as in Experiment 3 with this dog, and necropsy showed them to be entirely patent and with no evidence of thrombosis.

CLINICAL TRIAL, CASE 2.—March 16, 1913: G. S., a girl aged 10, was admitted to the hospital March 2, 1913, with severe scarlet fever of a septic type. There was a profuse nasal discharge and pronounced angina. A throat culture was negative for Klebs-Loeffler bacilli. March 5 130 c.c. of antistreptococcus serum were given without effect. The patient became rapidly worse, and on March 6, the condition being desperate, it was planned to make a transfusion with the blood of a convalescent scarlet-fever patient who volunteered for the purpose. One hundred and fifty c.c. of blood were quickly and without difficulty removed from the median basilic vein of the donor, and an attempt was made to transfuse this into the median basilic vein of the patient. This latter blood-vessel was insufficiently exposed to view and took a turn just above the upper extremity of the skin incision. Dripping of blood from the cannula further interfered with the accurate introduction of the cannula, which was a sharp one, and the vein was completely penetrated several times before its canal was finally entered. About 20 c.c. was eventually delivered, and although the blood remaining in the cannula appeared perfectly fluid, the length of time which had elapsed, about fifteen minutes, made it seem somewhat risky to continue the procedure beyond that time. A further injection of blood was therefore abandoned. The blood clotted in the cannula at about nineteen minutes, and began to clot in the cylinder at twenty-two minutes.

There was, of course, no effect to be anticipated from so small an amount of blood, and the operation had to be reckoned a failure. The patient died March 7 and no necropsy was allowed. The apparatus used in this operation was the same as noted under Experiment 4.

EXPERIMENT 5.—March 17, 1913: *To test action of cannula sleeve as an improvement in technic.*—Dog 4, male, 11.65 kg. Ether anesthesia. Aseptic precautions. Both femoral veins exposed.

Apparatus: a 200 c.c. graduated pipet with a special tapered cannula. Paraffin coating, mixture 10. An elastic cannula sleeve was contrived by using a piece of fine rubber tubing 1 cm. in length. This was held by clamping it longitudinally in a Carrel serrated clamp, and it was dipped in sterile liquid paraffin prior to use.

The right femoral vein was entered with the sleeve in position proximal to the shoulder of the cannula, and 140 c.c. of blood was aspirated as fast as could be obtained from the vein. As the cannula was removed, the sleeve was pushed into a position distal to the shoulder, thus covering the opening of the cannula. No dripping ensued. The cannula was now entered as far as the sleeve through the wall of the recipient vein, the sleeve was retracted proximally to the shoulder and the cannula pushed on into the vein up to the shoulder, allowing

the escape of only a few drops of blood. One hundred and thirty-five c.c. of blood were allowed to run from the pipet by gravity assisted by gentle blowing. The time of transfer was four minutes fifteen seconds. No ligatures were necessary; the skin was sutured and a collodion dressing applied. The dog was allowed to come from under the anesthetic and made a good recovery.

Observations on the coagulation time of the blood in this experiment will be found in Table 1.

TABLE 1.—Blood Coagulation Time. Experiment 5

	Temp. C.	Time	Occurrence of Clot
Preliminary coagulation time...	37	2′ 30″	None.
	37	2′ 45″	Firm.
Blood dripping from cannula after withdrawal from vein, 7′ 35″.	37	20″	None.
	37	1′ 00″	Partial.
	37	1′ 10″	Firm.
13′ 45″	44	30″	None.
	44	1′ 15″	Partial.
	44	1′ 30″	Firm.
18′ 35″	43	1′ 00″	Very slight.
	43	1′ 45″	Partial.
	43	2′ 15″	Firm.
21′	42	1′ 00″	Partial.
	42	1′ 30″	Partial.
	42	2′ 00″	Firm.
25′ and 30′.....	Blood still dripped from cannula; coagulation time not taken.		
35′	Blood did not drip from cannula, but could be easily blown through.		

It should be noted in regard to these determinations, which were by the Biffi-Brooks method, that the loopfuls of blood obtained for observation varied considerably in volume, owing to the fact that the blood was of necessity allowed to drip from the cannula on the platinum loops, instead of being collected in the usual manner by passing the loops over the blood. This, of course, invalidates the accuracy of this method for determining the clotting time of blood dripping from the cannula. The application of the cannula sleeve in this operation was found very satisfactory and effective.

Experiment 6.—April 1, 1913: *Illustrating error of technic in coating.*—Dog 5, male, 13.6 kg. Ether anesthesia. Aseptic precautions. Both femoral veins exposed.

Apparatus: a 200 c.c. pipet and a 150 c.c. pipet provided with tapered cannulas and cannula sleeves as in Experiment 5, and coated with paraffin mixture 10. After the second coating both cannulas were briefly heated over the free flame of a Bunsen burner to reduce to a minimum the amount of wax within their lumen. (This was later recognized as an error of technic.)

A preliminary test of the dog's blood gave a coagulation time of one minute thirty-five seconds at 37 C. (98.6 F.) by the method of Dale and Laidlaw. This method was chosen as being best suited to the conditions of the investigations,

and was especially satisfactory on account of the sharply defined end-point of the determination.

With the first pipet about 60 c.c. of blood were removed from the right femoral vein and injected into the left femoral vein. Clotting occurred shortly after the introduction of the cannula into the recipient vein. The clot was removed, and at eight minutes the injection was resumed, and all but a small remainder was delivered without further clotting. At nine minutes the coagulation time of the blood reserved in the pipet was one minute twenty-five seconds at 37 C. (Dale-Laidlaw).

With the second pipet a second transfusion was attempted from the right femoral to the left femoral veins, and clotting again occurred in the cannula shortly after its introduction into the recipient vein. This clot was removed, and about 80 c.c. of blood were injected into the vein at four minutes, the remainder being reserved in the pipet for observation. At eight minutes the coagulation time of blood dripping from the mouth of the canula was found to be one minute twenty-five seconds at 37 C. (98.6 F.). Between nine and ten minutes it was found that the blood had again clotted in the cannula, but that in the cylinder remained fluid for more than thirty minutes. Some of this was removed from the cylinder at thirty minutes and tested for coagulation time. It was found to be in two minutes ten seconds at 30 C. (86 F.).[4] The wounds were sutured, dressing applied and the dog allowed to come from under the anesthetic. Good recovery.

EXPERIMENT 7.—April 3, 1913: *To test the correctness of conclusions from Experiment 6 as to technic of coating.*—Dog 5, male, 13.6 kg. (dog used in experiment 6). Ether anesthesia. Aseptic precautions. Both external jugular veins used.

Apparatus: Two pipets of 120 c.c. and 200 c.c. capacity, respectively, provided with tapered cannulas, carefully coated at the proper temperatures and without flaming; paraffin coating 12.

The right jugular vein was entered against the current and about 80 c.c. of blood were removed and transferred to the left jugular vein with the current, 2 to 3 c.c. being allowed to remain in the pipet. The time of transfer was two minutes ten seconds. Preliminary coagulation time was one minute thirty seconds at 37 C. by the Biffi-Brooks method; one minute twenty seconds by the Dale and Laidlaw method at the same temperature. At sixteen minutes after removal from the vein the blood remaining in the pipet was allowed to drip from the cannula and the coagulation time was found to be one minute twelve seconds at 37 C. by the Dale-Laidlaw method.

The left jugular vein was entered with the second pipet, against the current, and 150 c.c. of blood were removed. All but 4 or 5 c.c. of this was transferred to the right jugular vein. The blood was withdrawn from the vein as rapidly as it would flow, the time being one minute forty seconds. The heart's action became coincidently very much accelerated, as also the respiration. The blood was more slowly introduced into the right jugular vein to avoid overdistention of the right auricle. The time was three minutes forty-five seconds. The amount was 145 c.c. The total time of transfer was five minutes thirty seconds. During the reintroduction of the blood the pulse and respiration fell to about the same rate as before its removal. Coagulation time of blood dripping from the cannula after the operation was as follows:

At 6 to 7 minutes after withdrawal from vein:

1 minute 10 seconds to 1 minute 30 seconds at 37 C. by the Biffi-Brooks method.

1 minute 10 seconds at 37 C. by the Dale-Laidlaw method.

At 18 minutes the coagulation time was 40 seconds at 37 C. by the Dale-Laidlaw method.

4. Corrected for temperature according to Bürker's curve for human blood[3] this would be one minute forty-four seconds at 37 C.

At 25 minutes the blood had clotted in the cannula, but was still fluid in the cylinder.

Observation of the blood remaining in the pipet was not continued after twenty-five minutes. The dog was killed at the end of the experiment. Necropsy showed a skin infection of wounds in the groins from former operation. The femoral veins used in the previous transfusion were patent and contained fluid blood.

EXPERIMENT 8.—April 7, 1913: *To test further the comparative effects of proper and improper method of second coating.*—Dog 6, male, 11 kg. Ether anesthesia.

Apparatus: same as used in the last experiment. Two pipets used. Pipet 1 received careful attention in its second coating, especially as to proper temperature (60 to 61 C.; 140 to 141.8 F.). Pipet 2 received its second coating improperly as in Experiment 6, the cannula being gently heated over a free flame to allow the excess of paraffin to be blown out.

Both femoral arteries and external jugular veins were exposed. Using Pipet 1, 200 c.c. of blood were taken from left femoral artery in one minute twenty seconds, the artery was clamped and one minute later the cannula was introduced into the left jugular vein. All but 8 c.c. of the blood was injected; time, three minutes forty seconds. Total time of transfer six minutes forty-five seconds. Preliminary clotting time of dog's freshly shed blood was one minute twenty seconds at 37 C. by the Dale-Laidlaw method. At thirty-four minutes forty-five seconds the blood reserved in the pipet for observation dripped from the cannula when the sleeve was retracted, and its coagulation time at 35.6 C. was forty seconds (Dale-Laidlaw). At forty-two minutes forty-five seconds blood still dripped from the cannula when the sleeve was retracted, and its coagulation time was 30 seconds at 35 to 36 C. (95 to 96.8 F.) by the Dale-Laidlaw method. At forty-four minutes forty-five seconds the blood had clotted in the cannula, but was still fluid in the cylinder, and remained so until sixty minutes forty-five seconds, when it had just started to clot.

With Pipet 2, 215 c.c. of blood were taken from the right femoral artery in one minute fifteen seconds, and the greater part of this was transferred to the right jugular vein. The total time was five minutes forty-five seconds. At ten minutes the blood had clotted in the lumen of the cannula. The clot was removed at fourteen minutes forty-five seconds, and the blood which then dripped away clotted in twenty seconds at 37 C. (Dale-Laidlaw). The blood again clotted in the cannula immediately, but remained fluid in the cylinder until twenty-two minutes, when it began to clot. The dog was killed at the end of the experiment.

EXPERIMENT 9.—April 16, 1913: *Illustrating effect of trauma by stretching and abrasion of intima.*—Dog 7, male, 6.6 kg. Ether anesthesia. Aseptic precautions. The same apparatus as used in Experiment 8. Preliminary coagulation time at 37 C., one minute twelve seconds by the Dale-Laidlaw method. Right femoral and saphenous veins exposed. A part of the latter was selected for entry which appeared about half the diameter of the cannula. This was, nevertheless, easily entered by stretching, and about 80 c.c. of blood were slowly aspirated. The slow withdrawal of blood was due to the small size of the vessel and the pronounced valve-action of the stretched wall against the mouth of the cannula. The cannula was removed from the saphenous vein at five minutes twenty seconds, and was then introduced into the femoral vein. No blood would pass, and the cannula was immediately withdrawn and found to contain a long clot. The clot was removed with a small forceps and the cannula again introduced into the femoral vein at nine minutes thirty seconds after entry into first vein. Half the amount of blood in the pipet, about 40 c.c., was then injected and at ten minutes ten seconds a second clot formation occurred which blocked the cannula. This was removed with difficulty, and no attempt was made to inject the blood remaining in the pipet. The vein punctures were ligated with fine catgut and the wound

closed in the usual manner with a collodion dressing. The dog was allowed to come from under the anesthetic and made a good recovery.

At twelve minutes after first withdrawal from the vein the blood remaining in the pipet showed a single string of fibrin, and the blood in the cannula had again clotted. At twenty-five minutes there were several long strings of fibrin apparent on rotating the pipet, but the rest of the blood was still fluid. At thirty-four minutes a solid clot had formed.

EXPERIMENT 10.—April 22, 1913: *To confirm the conclusions from last experiment.*—Dog 7 (dog used in Experiment 9). Ether anesthesia.

Apparatus is that used in Experiment 9. Two pipets with sharp-pointed, tapered cannulas. Paraffin mixture 24.

Preliminary clotting time of dog's blood forty-six seconds at 37 C. (Dale-Laidlaw). Left femoral and internal saphenous veins exposed, also both external jugulars.

With Pipet 1 having a larger tapered cannula, about 160 c.c. were taken from the right external jugular, against the current, in two minutes ten seconds, and about one-half of this was injected, against the current, into the left external jugular in one minute thirty seconds. The total time was four minutes. No difficulty was experienced. The blood dripping from the cannula was tested as follows:

At 9 minutes 30 seconds the coagulation time was 20 to 25 seconds at 37 C.

At 34 minutes the coagulation time was 1 minute 2 seconds at 34 C. (temperature correction negligible).

At thirty-four minutes there was some fibrin formation apparent in the blood in the cylinder, although the bulk of it was perfectly fluid. At forty minutes the blood in the cannula and cylinder had clotted firmly. With Pipet 2, which was fitted with the smaller tapered cannula, the left internal saphenous vein was entered. This vessel was much smaller in its normal diameter than the cannula, and the conditions of Experiment 9 were closely simulated; that is, the distention and flapping of the vein-wall against the mouth of the cannula. Aspiration was very slow, about 50 c.c. of blood being obtained in eight minutes fifteen seconds. A very small portion of this blood (about 10 c.c.) was injected into the left jugular, and at nine minutes thirty seconds the flow was stopped by a clot in the cannula. There was also observed at this time slight evidence of fibrin formation in the fluid blood remaining in the cylinder. At nineteen minutes thirty seconds the blood in the cylinder was still fluid, but with more strings of fibrin. At thirty-two minutes the blood was still fluid, but there was much fibrin formation. Observation was not continued further. The dog was killed at the end of the experiment.

EXPERIMENT 11.—April 28, 1913: *A variation of the last two experiments to determine the effect of making the recipient vein the traumatized vessel.*—Dog 8, male, 9.5 kg. Ether anesthesia. Apparatus, two pipets as used in Experiment 10. Paraffin coating 24. Preliminary coagulation time of dog's blood one minute seventeen seconds at 39 C. (102.2 F.) by the Dale-Laidlaw method. Right femoral, left internal saphenous and both external jugular veins were exposed.

Pipet 1 was introduced into the right jugular vein and 220 c.c. of blood withdrawn in one minute forty-five seconds. One minute elapsed in transferring to the right femoral, and 200 c.c. were injected into this vessel in one minute forty-five seconds, making the total time of transfusion four minutes thirty seconds. Both tributary and recipient veins were of ample size and no hindrance was met. Observations on coagulation of the 20 c.c. of blood remaining in the pipet were as follows:

At 21 minutes 22 seconds, flowed from cannula. Fluid in cylinder, no fibrin. Coagulation time 1 minute 55 seconds, 37 C.

At 25 minutes, clotted in cannula, fluid in cylinder, with some fibrin formation.

At 35 minutes, clotted in canula, fluid in cylinder, with much fibrin formation.

At 38 minutes, clotted in cannula, firm clot in cylinder.

Pipet 2 was introduced into the left jugular vein and 200 c.c. of blood withdrawn in three minutes forty-five seconds. The internal saphenous vein selected for the recipient vessel was very small and was much traumatized and distended in effecting an entrance. When the cannula was in place it was found that the blood could not be freely injected, even with considerable pressure. At eight minutes fifteen seconds the instrument was withdrawn and another unsuccessful attempt was made to inject the same vein at a more proximal point. This also permitted too slow a delivery on account of the small size of the vessel, and at nineteen minutes the vein was penetrated at its junction with the femoral, where there was a free opportunity for discharge, and about 150 c.c. of blood were then delivered from the pipet. At twenty-three minutes thirty seconds the blood was found to have clotted in the cannula and there was considerable fibrin formation in the cylinder. At twenty-five minutes more fibrin appeared and at thirty-three minutes a firm clot existed. The dog was killed at the end of the experiment. Necropsy showed no blood-clots in the right heart or in the pulmonary arteries.

Clinical Trial, Case 3.—April 29, 1913: E. M., a boy, aged 11, had osteomyelitis of the femur with general staphylococcus septicemia, which had run a chronic course since his admission to the hospital and an operation six weeks previously. Temperature reached 102 to 103 F. daily. Hemoglobin 30 per cent. *Staphylococcus aureus* was obtained from the blood-culture. An uncle had been immunized with vaccines derived from the infecting organism of the patient for the purpose of transfusing the staphylococcus-immune blood. The donor's and recipient's median basilic veins were exposed under local anesthesia and transfusion carried out with apparatus as used in Experiment 11. One hundred and fifty c.c. of blood were removed in two minutes fifty seconds, and 100 c.c. of the amount were injected in nine minutes. The recipient's vein was unusually small. The total time was thirteen minutes fifty seconds. The blood remaining in the pipet, reserving a very little for observation, was allowed to flow on sterile gauze for local application to the suppurating sinuses. At twenty minutes there was evidence of clot formation in the cannula and a few shreds of fibrin could be seen on agitating the blood remaining in the cylinder; at twenty-six minutes there was a fairly firm clot in both cylinder and cannula. May 9, ten days later, the patient's hemoglobin was 80 per cent., temperature practically normal and local condition improved.

DISCUSSION OF RESULTS

In the preliminary part of the experimental work, that is, up to Experiment 5, the main requirements of an efficient apparatus were realized. These essential features are: (*a*) rigid pipet, arranged for pneumatic aspiration and discharge, terminating in a tapered cannula with a smoothly walled channel, the point of the cannula being conical in shape and having an opening of sufficient size to provide a rapid flow of blood; (*b*) a smooth unbroken coating of a suitable paraffin mixture throughout the apparatus; (*c*) a means of closing the opening of the cannula at will, supplied by the obturating sleeve as described in Experiment 5.

In the course of further experimentation it was found that there were several errors of technic which materially affected the success of the operation, and which by proper attention could be avoided. The first of these errors was in the matter of coating the apparatus. In Experi-

ment 6, the clotting in the cannula was a bad feature and was evidently due to heating the cannula over the free flame after the second coating. In Experiments 7 and 8 this question was further tested and the conclusion was reached that a fairly low temperature at the second coating is essential in order to insure an intact wall of paraffin in the channel of the cannula, without which there is a tendency to clot formation in the cannula and also, to some extent, in the cylinder above.

TABLE 2.—BLOOD COAGULATION TIME IN CLINICAL CASES 1 TO 3, AND EXPERIMENTS 5, 7, 8, 10 AND 11*

Case and Experiment No.	Time of Occurrence of Clot Formation in Cannula	Time of Occurrence of Clot Formation in Cylinder
Clinical Case 1.....	15 to 20′	21′
Clinical Case 2.....	19′	22′
Dog 4, Exp. 5.....	35′	After 35′
Dog. 5, Exp. 7.....	25′	Still fluid at 25′
(Transf. B)		
Dog. 6, Exp. 8.....	44′, 45″	60′, 45″
(Transf. A)		
Dog 7, Exp. 10.....	34 to 40′	34 to 40′
(Transf. A)		
Dog 8, Exp. 11.....	25′	38′
(Transf. A)		
(Transf. B)	23′, 30″	33′
Clinical Case 3.....	20′	26′

* In Table 2 are placed the results of observations on the periods of time which elapsed before coagulation of the blood in the cannula and in the cylinder in those instances in which the conditions of the experiment can be considered normal; that is to say, in which no special factors were introduced to influence an early clot formation.

It was also demonstrated in Experiment 8 that arterial blood can be very quickly obtained by this method. Whether this would usually necessitate clamping and tying of the artery, or whether the rent in the arterial wall can be repaired so as to preserve a functionating vessel as with a vein, we are, so far as our experience goes, unable to say; but we believe that the use of arterial blood may prove to be a valuable application of the method in clinical practice.

Another important error, illustrated in Experiments 9, 10 and 11, was the mistake of inviting clot formation by allowing an undue access of thromboplastic substance from stretched and broken tissue. In Experiment 9 the small donating vein was considerably stretched, and

its intima was probably further damaged by flapping against the edges of the mouth of the cannula, with the result of an early and repeated clot formation. In Experiment 10 the blood from the traumatized vessel showed evidence of fibrin formation in the pipet at nine minutes thirty seconds as against thirty-four minutes in the control operation where no trauma was induced. In Experiment 11 the traumatizing of the recipient vein, on the other hand, though doubtless leading to a liberation of thromboplastin, did not produce the early clotting effect in the cannula which was observed when the donating vein was the injured vessel. The most probable explanation of this observation is that the current of outflowing blood from the cannula carried away from the instrument into the circulation, any thromboplastin which may have been formed at the site of puncture.

It is noticeable that there is a considerable range in the period of fluidity, the variation being from nineteen to forty-five minutes in the cannula, and from twenty-one to sixty minutes in the cylinder. The cause of this variation is a matter of speculation, but the most plausible explanation would seem to be that there are differences in the degree of manipulation and trauma incidental to each case, and that these differences resulted in a variation of the amount of thromboplastin set free. Among other possible factors it may be surmised that the vascular tissues of some animals are more friable than others, and that the thromboplastic substance in the tissue lymph of some individuals is more abundant or more active than in others. It should also be noted that in Dog 6, Experiment 8, Transfusion A, the comparatively long persistence of fluidity may have been due to a set of factors peculiar to this experiment, namely, that the vessel punctured was an artery, the blood arterial, and the speed with which it was obtained was very much greater than in the other experiments.

CONCLUSIONS

Generally speaking, a careful technic in the method of transfusion here described is of paramount importance, and should be based on two main principles. The first is that there shall be no lapse of the paraffin coating to act as a starting-point for the arrest and disintegration of the formed blood elements, or in whatever other way such a moistenable point may act in initiating a formation of thromboplastin. The second is that there shall be the least possible injury to the tissues of the donating vessel which are exposed directly to the transferred blood, lest there be, through such injury, an admixture of thromboplastin liberated with the tissue juices. The necessity for care in guarding against these two liabilities constitutes the one factor which militates against the simplicity

and wide usefulness of the method, and it must therefore be considered a disadvantage. The practical advantages may be summed up as follows:

1. An apparatus has been contrived which is compact, which may be easily and precisely manipulated with one hand, and which may be prepared in readiness for immediate use in an emergency.

2. The operation may be easily performed by a single operator without skilled assistance, and the requisite facility in surgical technic is possessed by anyone who is able to perform an ordinary intravenous saline infusion.

3. The arrangement for pneumatic aspiration and discharge of the blood affords a delicate and convenient means of control.

4. The use of the special stylets for puncturing the exposed vein-wall insures an entrance of the cannula on the first trial, and by this method only a small skin incision is necessary. The vessels used are neither divided nor tied off and the puncture hole is very small, so that subsequent function is unimpaired.

5. The flow of blood in the donor's and the recipient's veins is not interrupted at the site of operation, and the danger of clot formation in clamped vessels is therefore not encountered.

6. The amount of blood transfused and the rate of flow can be accurately observed.

7. The donor and recipient may be separated by any convenient distance, and the risks of tearing apart are eliminated.

8. The materials of the apparatus are glass, silver and asbestos, all of which can be sterilized by dry heat in an autoclave or in an ordinary oven.

In a more extensive test of this method of transfusion under varying clinical conditions, modifications of technic may be advisable. As the aim is to perfect a method of wide usefulness to the general practitioner, there are certain improvements still to be sought in the way of greater simplicity and facility. For instance, it would be desirable to work out a means of using the apparatus safely without a double paraffin coating, or possibly to dispense with a complete coating of the cylinder by a preliminary flushing of the whole apparatus with a solution of hirudin in normal salt solution. An improvement in technic would be realized if a simple device were provided for covering the mouth of the cannula during its passage into the donor's blood-vessel, so as to afford protection from contact with broken tissue at the point of puncture. From the indications of work already done toward this end, it is not improbable that some such improvements can be worked out. Meanwhile we believe that the results of our experiments have been of sufficient interest to

report, and that the method so far developed should have a more extensive clinical trial to determine its usefulness.

We wish here to express our thanks to Professor Frederic S. Lee for his kind interest in our work, and for valuable suggestions in the preparation of this paper.

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REFERENCES

In addition to the numbered references the following are referred to in the text:

Addis, T.: Jour. Infect. Dis., 1912, x, 200.

Brodie, T. G.: Jour. Physiol., 1900-1901, xxvi, 48.

Bürker, K.: Arch. f. d. ges. Physiol., 1912, cxix, 318.

Cooley and Vaughan: Jour. Am. Med. Assn., 1913, lx, 435.

Crile, G. W.: Hemorrhage and Transfusion, D. Appleton & Co., 1909.

Curtis and David: Jour. Am. Med. Assn., 1911, lvi, 35; 1911, lvii, 1453; Surg., Gynec. and Obstet., 1912, xv, 476.

Dale and Laidlaw: Jour. Path. and Bacteriol., 1912, xvi, 351.

Duke, W. W.: Jour. Am. Med. Assn., 1910, lv, 1165; Jour. Exper. Med., 1911, xiv, 265; The Archives Int. Med., 1913, xi, 100.

Edelberg, M.: Arch. f. exper. Path. u. Pharmakol., 1880, xii, 283.

Esmarch, F.: Handbuch der Kriegschirurgischen Technic, 1877, p. 165; Surgeon's Handbook, 1888, Eng. transl. 3d Ger. ed., p. 213.

Esmarch and Kowalzig: Surgical Technic, 1901, Eng. transl. by Grau & Sullivan, p. 278.

Falta, W., and Fleming, G. B.: München. med. Wchnschr., 1911, lviii, 2649.

Fuld, E.: Zentralbl. f. Physiol., 1903, xvii, 529.

Genou, O.: Ann. de l'Inst. Past., 1901, xv, 232.

Howell, W. T.: Am. Jour. Physiol., 1910, xxvi, 453; 1911, xxix, 187; 1912, xxxi, 1.

Hürter, J.: Beihefte z. med. Klinik, 1911, No. 12.

Köhler, A.: Inaug. Diss., Dorpat, 1877.

Lindeman, E.: Rep. Ped. Sect., New York Acad. Med., April 10, 1913.

Moldovan, J.: Deutsch. med. Wchnschr., 1910, xxxvi, 2422.

Morawitz, P.: Ergebn. d. Physiol., 1905, iv, 307; München. med. Wchnschr., 1907, liv, 767.

Moritz, F.: München. med. Wchnschr., 1911, lviii, p. 395.

O'Connor, J. M.: München. med. Wchnschr., 1911, lviii, 1439; Arch. f. exper. Path. u. Pharmakol., 1912, lxvii, 195.

Pike, Guthrie and Stewart: Jour. Exper. Med., 1908, x, 371.

Poiseuille: Ann. de Chimie et de Physique, 1843, Series 3, vii, 59.

Risley and Irving: Boston Med. and Surg. Jour., 1912, clxvi, 956.

Schultz, W.: Deutsch. Arch. f. klin. Med., 1905, lxxxiv, 541.

Sollmann, T.: Am. Jour. Physiol., 1905, xiii, 291.

Stevens, L. T., and Lee, F. S.: Studies fr. Biol. Lab. Johns Hopkins Univ., 1884, iii, 99.

Stewart, H. A., and Harvey, S. C.: Jour. Exper. Med., 1912, xvi, 103.

Whipple, G. H.: The Archives Int. Med., 1912, ix, 365.

Ziemssen, H.: Verhandl. d. Kong. f. inn. Med., No. 11, Leipsic, 1892, 166; Deutsch. Arch. f. klin. Med., 1892, l, 491; München. med. Wchnschr., 1894, xli, 349; 1895, xlii, 301.

THE CONDITION OF THE BLOOD IN HEMOPHILIA, THROMBOSIS AND PURPURA*

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During the past two years I have made systematic examinations of the blood in patients suffering from various forms of diseases of the blood, hemorrhagic and thrombotic, with special reference to the variations in the amount of antithrombin and prothrombin. The most significant results have been obtained in cases of hemophilia and in so-called idiopathic or spontaneous thrombosis. The chief object of the present paper is to report the findings in these two latter conditions.

METHODS

The specimens of blood used for examination were obtained in all cases from one of the superficial veins of the arm by means of a graduated syringe (Luer form). The syringe was sterilized previously with boiling water and before inserting the needle into the vein it was filled with sterile salt solution (sodium chlorid 0.9 per cent.) by partially filling the syringe and then expelling the solution so as to leave the needle full. The object of this precaution was to avoid the bubble or two of air in the needle which otherwise interfered with the accuracy of the reading of the amount of blood taken. Usually 8 c.c. of blood were taken for each experiment and as soon as possible the portion to be examined for antithrombin and prothrombin, namely, 4 c.c., was emptied into a centrifugal tube containing 0.5 c.c. of a 1 per cent. solution of sodium oxalate (made up in a 0.9 per cent. solution of sodium chlorid). After mixing by inverting the tube this specimen was centrifugalized at a high speed to obtain a clear plasma. The plasma, which in human blood is always deeply colored, yellowish green, was pipetted off and examined as follows:

Antithrombin.—To determine the relative amount of antithrombin in the oxalated plasma of the patient it was compared always with a similar specimen taken at the same time from a normal person. The two plasmas were heated in a water-bath slowly to just 60 C. At this temperature (53 to 60) the fibrinogen is all precipitated and the thrombin and prothrombin are destroyed, while the antithrombin on the contrary is not affected, or at least is affected as little as possible consistent with the necessity of removing the fibrinogen and thrombin. Only at temperatures above 65 C. does the antithrombin show a distinct diminution in strength.

To test the antithrombin in the heated plasmas they were added in known amounts to varying mixtures of thrombin and fibrinogen. The thrombin was prepared in quantity by a method previously described[1] and was kept in dry condition in watch crystals, each crystal containing the same amount. For each test

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1. Howell: Am. Jour. Physiol., 1910, xxvi, 453. For modification see also same, 1913, xxxii, 264.

the contents of one of these crystals was dissolved in water (4 to 8 c.c.).[2] For fibrinogen solutions I have not found it convenient to use so-called pure fibrinogen prepared by the method of Hammarsten, since it is not possible by this method to obtain solutions of uniform concentration or properties. The repeated precipitations of the fibrinogen denatures it in part. In place of such solutions I have used the oxalated and dialyzed blood plasma of dogs or cats. To get this material a fasting animal was bled into an oxalate solution, nine parts of blood to one part of a 1 per cent. solution of sodium oxalate made up in sodium chlorid, 0.9 per cent. This mixture was centrifugalized, the plasma was pipetted off and the excess of oxalate was removed by dialyzing in collodion tubes for twenty-four hours against a solution of sodium chlorid 0.9 per cent. The plasma thus obtained does not clot spontaneously, but coagulates promptly on the addition of a little thrombin. A large quantity of this material was prepared from one animal and it was dried in watch crystals, 3 to 5 c.c. to a crystal, in a current of cold air from an electrical fan. When needed the contents of one or more of these crystals was dissolved in a known amount of a 0.9 per cent. solution of sodium chlorid. The solution obtained is quite clear. In the tests described below these solutions of dried plasma will be spoken of as fibrinogen solutions. Ten drops of this solution when mixed with 2, 3, 4 and 5 drops of the thrombin solution clotted in from two to five minutes. To determine the antithrombin in the heated oxalated plasmas described above the following mixtures were made:

1. 10 drops fibrinogen sol. + 1 drop heated plasma + 2 drops thrombin solution.
2. 10 drops fibrinogen sol. + 1 drop heated plasma + 3 drops thrombin solution.
3. 10 drops fibrinogen sol. + 1 drop heated plasma + 4 drops thrombin solution.
4. 10 drops fibrinogen sol. + 1 drop heated plasma + 5 drops thrombin solution.

Inasmuch as the effect of antithrombin on thrombin varies greatly with the time allowed for their interaction it is necessary in these experiments to add first the drop of heated plasma to the 2, 3, 4 and 5 drops of thrombin solution and to allow these mixtures to stand for a definite time before adding the solutions of fibrinogen. The time interval adopted in all my experiments for this action of the antithrombin and thrombin was fifteen minutes, and care was taken to see that this interval was identical within a second or two in all comparative tests. At the expiration of the fifteen minutes the fibrinogen solution was added and the time of coagulation of each specimen was observed. The mount of antithrombin contained in one drop of heated normal plasma was sufficient, in the solutions used, to delay the action of two drops of thrombin on the fibrinogen usually for an hour or more, or to prevent clotting altogether. In the specimens containing 3, 4 and 5 drops of thrombin the delay was proportionally less marked, the specimen containing 5 drops of thrombin clotting usually in five minutes. It is easy by this method to determine the relative amounts of antithrombin in different specimens of blood. In bird's plasma or the plasma from a peptonized dog the antithrombin exists in relatively large amounts so that a drop of the heated plasma may inhibit completely the action of such amounts of thrombin as are here considered.

In determining the time of coagulation in the different specimens the tubes containing the mixtures were examined, usually at intervals of five minutes, by gently inclining the tubes. When the thrombin was in distinct excess the contents of the tubes set to a firm clot, but when the thrombin was nearly neutralized by the antithrombin it was difficult or often impossible to ascertain when clotting occurred, since under such circumstances the clot forms in several stages. First, a delicate veil which on agitation shrinks to a small membrane while later a more solid gelatinous clot may form.

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2. The solutions of thrombin should not be filtered since the thrombin is absorbed to some extent by the filter paper.

Specimens in which the thrombin and antithrombin existed in this balanced proportion were useless for comparative purposes, and in such cases it was necessary to rely on the specimens containing more thrombin in which the clotting occurred promptly.

By way of illustration of the method, the results of one of the comparisons made between hemophilic and normal blood may be quoted.

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibrinogen Drops	Coagulation Minutes
		NORMAL INDIVIDUAL		
1	2	15	10	160
1	3	15	10	10
1	4	15	10	10
1	5	15	10	5
		HEMOPHILIC BOY		
1	2	15	10	*
1	3	15	10	35-40
1	4	15	10	15
1	5	15	10	10

* No clot in seven hours.

This method has been applied to the examination of a very large number of specimens of human blood, normal and pathological. It has been found that while the content in antithrombin of normal blood exhibits certain fluctuations the variations are not large and do not necessarily run parallel to the coagulation time, owing to the fact that this latter time depends upon the balance between the thrombin and the antithrombin. In pathological bloods no significant constant variation in the amount of antithrombin has been detected except possibly in the condition known as idiopathic thrombosis.

Prothrombin.—In order to arrive at an idea of the relative amount or relative efficacy of the prothrombin in the plasmas examined I have adopted the procedure of adding to the oxalated plasma the optimum amount of calcium chlorid, that is to say, the amount that causes the most rapid clotting. This method was suggested by the observation that in a successful peptonized plasma (dog) addition of calcium chlorid does not cause clotting even when the plasma has been diluted previously with water. If, however, such a plasma is first oxalated and then calcium chlorid is added in proper amounts, clotting occurs readily. For some reason, not easily understood at present, the act of oxalating, that is, the decalcifying of the solution, intensifies the activation caused by the subsequent addition of calcium, so that the end result is apparently a greater production of thrombin, sufficient in fact to overcome the antithrombin and cause clotting. The alternative hypothesis that suggests itself, namely, that the process of oxalating may weaken the antithrombin, is easily shown to be erroneous. In some way the decalcification and subsequent calcification serve to bring into active form the maximum supply of prothrombin present in the blood. Whether or not this interpretation of the reaction is correct the simple procedure described has brought out a very constant and striking difference between normal and hemophilic blood. The reaction was carried out as follows: Five drops of oxalated plasma were placed in each of four tubes and to these were added in series, 2, 3, 4 and 5 drops of a 0.5 per cent. solution of calcium chlorid, with the idea that in one of the tubes the optimum concentration of calcium would be obtained. With the amount of plasma used clotting occurred first in the tubes containing 2 or 3 drops of calcium chlorid. With one drop the clotting occurred slowly or not at all, owing to an insufficiency of calcium, while in the tubes with 4 or 5 drops the clotting was somewhat slower than in the tubes with 2 or 3 drops, owing to too great an excess of calcium. Tested by this method the clotting of normal blood plasma is remarkably uniform, varying between nine and twelve minutes. In the plasmas

of hemophilic blood, on the contrary, the time of clotting is greatly prolonged. This fact, indeed, has been noted by Addis,[3] although he does not seem to have used the reaction in any extensive way. I have employed the reaction, as described above, for a large series of bloods to throw light on the amount or efficacy of the prothrombin, when parallel tests have established the fact that there is no variation in the amount of antithrombin in the bloods examined.

RESULTS

Purpura.—At different times in the course of this work specimens of blood have been obtained from patients suffering from various forms of purpura, including one case of severe purpura hemorrhagica. The time of coagulation of these bloods, when obtained by venepuncture, did not vary distinctly from normal, and the content of the plasmas in antithrombin and prothrombin was also within the limits found for normal bloods. It does not seem desirable at present to publish the details of these negative findings, since this paper deals especially with hemophilia and thrombosis. Duke[4] has published some interesting observations on cases of purpura hemorrhagica which show that the coagulation time may be normal while the bleeding time is greatly prolonged. By the latter term he designates the time that a small wound will continue to bleed, as determined by pressing against it a bit of filter paper at definite intervals of time. He has connected the increased bleeding time in purpura with a marked deficiency in platelets, in consequence of which platelet thrombi fail to form in the wounded vessels. My work throws no light on this point, but it does demonstrate that severe purpura hemorrhagica may exist without any detectable abnormality in the factors concerned in the clotting of the blood. The tendency to bleeding in these cases cannot be referred apparently to a deficient power of coagulation.

Hemophilia.—I have had the opportunity of examining with care two cases of undoubted hereditary hemophilia and a third case of a young boy in which no history of inheritance could be obtained. The history of these cases is as follows:

REPORT OF CASES

CASES 1 and 2.—Joseph Y., aged 12 years, and Jesse Y., aged 8 years, sons of Joseph Y. of Baltimore, a Russian Jew. The hemophilic tendency in these children was inherited from the mother. She stated that three of her brothers died from hemorrhage; one at 17 years of age as the result of an operation on the tonsils; one at 6 years from a cut on the face made accidentally by a playmate, and one at the time of circumcision. She states also that a cousin, daughter of her father's brother, has married and has hemophilic boys. An effort to locate this latter family was not successful. In the present family of Joseph Y. there

3. Addis: Jour. Pathol. and Bacteriol., 1911, xv, 436.

4. Duke: Jour. Am. Med. Assn., 1910, lv, 1185; Bull. Johns Hopkins Hosp., 1912, xxiii, 145.

are seven children; three boys, Joseph, 12 years, Jesse, 8 years and Fred, 5 years, all markedly hemophilic, and four girls none of whom have exhibited any tendency to bleed. Great difficulty from bleeding has been experienced at various times with the three boys. All have suffered from serious hematomata due to accidents in playing. Joseph at the time of circumcision is said to have bled for a week. At 4 years of age he was brought to the Johns Hopkins Hospital with hemorrhage caused by biting the tongue while eating an apple. The hemorrhage, at first profuse, lasted nearly a week. It was partially controlled by cauterizing with lunar caustic. Parents gave a history of bleeding spells in the boy from slight injuries on four or five occasions. The coagulation time as then recorded was only six to twelve minutes. The method is not stated but probably the blood was taken by puncture through the skin and the result is therefore not reliable. He has been a patient at the hospital since this time on several occasions in connection with joint troubles. Fred when 3½ years of age was taken to the Hebrew Hospital, Baltimore, on account of a persistent hemorrhage from the tonsils supposed to be due to an accident. Bleeding continued for several days and was controlled finally or ceased finally after an injection of horse serum (8 c.c.)

In the experiments here reported only Joseph and Jesse were used as they were old enough to come to the laboratory and could be used conveniently for the operation of venepuncture.

CASE 3.—A. H. S., 4 years old, patient in the Harriet Lane Home of the Johns Hopkins Hospital. Since his third month difficulty has been experienced with bleeding from small cuts, and injuries of any kind have been followed by "black and blue" areas in the region involved. At the time of admission to the hospital—March 25, 1913—the child was very anemic: red blood-cells, 1,730,000; white blood-cells, 15,300; Hb. 33 per cent.; platelets apparently normal, although no count was made. Large purpuric areas existed on right arm and leg, right shoulder, left tibia and right cheek. Right arm, hand and shoulder much swollen; right leg also swollen. The child remained in the hospital until May 1, 1913, and showed very marked improvement. A blood count made April 15, showed red blood-cells 4,270,000; white blood-cells 13,000 and Hb. 80 per cent. On three occasions human blood serum was injected subcutaneously; on April 12, 10 c.c.; April 14, 14 c.c., and April 24, 15 c.c. Through the kindness of Dr. John Howland I was given an opportunity to examine the blood on two occasions; once, the day after admission to the hospital and once just before his discharge. On each occasion the specimens of blood were obtained for me by Dr. W. L. Moss to whose kindness and skill I have been much indebted throughout this work.

COAGULATION TIME OF THE HEMOPHILIC BLOOD

The coagulation time was determined on specimens of 2 or 4 c.c. of blood obtained directly from the vein by means of the sterilized syringe and expelled at once into wide tubes (diameter 21 mm.), which had been cleaned carefully with a bichromate acid mixture. The clotting time was estimated up to the time that the clot was firm enough to allow the tube to be inverted. Comparisons were always made with specimens of blood taken from normal individuals by the same method. Tested by this method the time of clotting of normal blood varies usually between twenty and forty minutes. The time shown by the hemophilic blood at different periods was as follows:

Nov. 2, 1912.....	Joseph Y.....	Clot apparent in 3 hours, complete in 4 hours.
	Jesse Y.....	Clot apparent in 3 hours, complete in 4 hours.

Dec. 21, 1912.....	Joseph Y.....	Clot apparent in 4 hours, complete in 5 hours.
	Jesse Y.....	Clot apparent in 4 hours, complete in 5 hours.
Jan. 18, 1913.....	Jesse Y.....	Clot apparent in 3 hours, complete in 4 hours.
April 19, 1913.....	Joseph Y.....	Clot apparent in 4 hours, complete in 5 hours.
	Jesse Y.....	Clot apparent in 4 hours, complete in 5 hours.
April 28, 1913.....	Joseph Y.....	Clotted between 2 and 2½ hours.[5]
May 17, 1913.....	Joseph Y.....	Clotted in 3½ hours.
June 14, 1913.....	Joseph Y.....	Clotted in 4 hours.
March 26, 1913.....	A. H. S.....	Clotted between 2½ and 3 hours.
May 1, 1913.....	A. H. S.....	Clotted between 3 and 4 hours.

It is apparent from these data that in the three cases examined there was a marked delay in the spontaneous coagulation of the hemophilic blood, such as has been reported by several other observers. So far as could be determined from the examinations made of the blood of the brothers Y., extending over a period of eight months, there was at no time an approach to normal, and in fact but little indication of any variation. The deficient coagulability was due to some permanent alteration in the properties of the blood. It is noteworthy in the case of A. H. S., that in spite of the fact that he had received during his stay in the hospital three injections of human serum and that his general condition had improved so greatly, the coagulation time, at the end, was as long or longer than when he first came into the hospital. In regard to the coagulation time of blood, it should be emphasized that errors may arise easily if the technic of obtaining the specimens fails in any respect. Constant and reliable results are obtained only in those cases in which the needle of the syringe enters the vein readily on the first puncture. When the vein is missed or transfixed and the lumen is found only after several trials, there is a likelihood that the specimen of blood may contain some tissue-juice, and therefore clot more rapidly than it would alone. This effect was shown very distinctly on one occasion with Jesse Y. On the first attempt the needle missed the vein, and only after several trials was it possible to draw about 2 c.c. of blood. When emptied into a tube this specimen clotted in ten minutes. A specimen of 8 c.c. was then obtained from the vein of the other arm. The technic was good, and a specimen of 2 c.c. placed in a tube clotted in the usual time, namely, between four and five hours.

No difficulty from hemorrhage was experienced in taking blood from the hemophilic patient, provided the vein was not wounded. On two

5. In this case 1 c.c. only was taken for examination, and there is a probability that some tissue juice was mixed with this specimen, since difficulty was experienced in getting into the vein.

occasions when the needle did not enter promptly, and there was probably some laceration of the vein, there developed later a somewhat extensive purpuric area which persisted for a long period.

EFFECT OF THROMBOPLASTIC SUBSTANCE AND OF CALCIUM ON THE CLOTTING OF HEMOPHILIC BLOOD

As stated above, admixture with thromboplastic material of the tissues accelerates greatly the time of clotting. On several occasions this result was obtained with the active principle of the tissue extracts; that is to say, with the phosphatid (kephalin) extracted from brain tissue as described in a previous paper.[6] In one experiment the kephalin was dissolved in a 6 per cent. solution of dextrose and a control was made with a similar solution of dextrose without kephalin. The kephalin caused a marked acceleration in the clotting of both normal and hemophilic blood.

Normal blood: 1 c.c. blood plus 1 c.c. dextrose solution (6 per cent.) clotted in 10 minutes.
1 c.c. blood plus 1 c.c. of dextrose solution containing kephalin clotted in five minutes.

Hemophilic blood (Joseph Y.): 1 c.c. blood plus 1 c.c. dextrose solution clotted between two hours, ten minutes, and three hours, thirty minutes.
1 c.c. blood plus 1 c.c. dextrose solution containing kephalin clotted in ten to eleven minutes.

A similar result was obtained with specimens taken from Jesse Y.

In a second experiment the coagulation time of a mixture of blood with kephalin was compared with that of the undiluted blood. The specimens containing the kephalin were placed in narrow centrifugal tubes which would tend also to shorten the time.

Coagulation time of 2 c.c. blood: Normal, 30 minutes; Joseph Y., four to five hours; Jesse Y., four to five hours.

Coagulation time of 2 c.c. blood plus 1 c.c. dextrose solution containing kephalin: Normal, four to five minutes; Joseph Y., twelve minutes; Jesse Y., eleven minutes.

Similar results were obtained in a third experiment, in which the kephalin was added in aqueous solution, and in which consequently there was considerable hemolysis of the blood.

It is stated that the content in calcium of the hemophilic blood is normal (Nolf[7]), and that addition of calcium chlorid does not hasten the time of coagulation (Morawitz and Lossen[8]). In my experiments it was noted that the oxalated hemophilic blood gave a good deposit of

6. Howell: Am. Jour. Physiol., 1912, xxxi, 1.

7. Nolf: Eine neue Theorie der Blutgerinnung, Ergebn. d inn. Med., 1913, x, 275.

8. Morawitz and Lossen: Deutsch. Arch. f. klin. Med., 1908, xciv, 110.

calcium oxalate on centrifugalization, but the deposit to the eye seemed less than that obtained from similar specimens of normal blood. An attempt was made to determine the amount of calcium in small specimens of the blood (8 c.c.), but the results were unsatisfactory. In a single experiment it was found that addition of calcium chlorid to the hemophilic plasma hastened somewhat the time of coagulation, as follows:

2 c.c. hemophilic plasma (Joseph Y.), coagulation time = four to five hours.

1 c.c. hemophilic plasma + 3 drops $CaCl_2$, ½ per cent., coagulation in two hours, thirty minutes.

1 c.c. hemophilic plasma + 6 drops $CaCl_2$, ½ per cent., coagulation in two hours, ten minutes.

ANTITHROMBIN IN HEMOPHILIC BLOOD

Examinations were made of the amount of antithrombin by the method previously described. In the case of the brothers Y., these examinations were made at irregular intervals during a period of several (eight) months, the blood being compared each time with a specimen of normal blood. In all cases the examination was made as soon as possible after taking the specimen from the vein, since experience had shown that when the blood is kept there is a gradual deterioration in the amount of antithrombin. The results of these comparisons are given in the accompanying table. It will be understood that the procedure was as previously described, that is to say, the clear plasma of the blood was heated to 60 C. and filtered. One drop of this heated plasma was then added to 2, 3, 4 and 5 drops of a thrombin solution, and, after an interval of fifteen minutes, ten drops of the fibrinogen solution (dried plasma) were placed in each tube. Owing to variations in the strengths of the thrombin solutions and fibrinogen solutions used, the different experiments are not comparable among themselves. In each experiment the antithrombin in the hemophilic plasma is to be compared with the normal blood taken at the same time and submitted to the same procedure.

Examination of these results shows that in general the amount of antithrombin in the hemophilic blood was somewhat greater than in the normal specimen with which it was compared. The excess, however, was not large and in some cases was not distinctly shown (experiments of December 21, April 19, April 28, May 17). Since in these latter cases the long coagulation time was still exhibited by the blood, it seems most probable that the characteristic delay in coagulation shown by hemophilic blood cannot be referred to an increase in the absolute amount of antithrombin present in the blood. As will be shown, however, in the next paragraph, there is good reason to believe that in these bloods there is always a relative excess of antithrombin, which is quite sufficient to account for the prolonged period of coagulation.

TABLE 1.—Results of Examination for Antithrombin in Hemophilic Blood

Date	Name	Thrombin in Drops	Time of Coagulation
Oct. 19, 1912.....	Joseph Y. (hemophilic)	2	8 to 15 hours.
		3	45 to 50 minutes.
		4	20 minutes.
		5	15 minutes.
	John S. (normal)	2	2 to 8 hours.
		3	30 to 35 minutes.
		4	10 minutes.
		5	10 minutes.
Nov. 2, 1912.....	Joseph Y. (hemophilic)	2	4 to 18 hours.
		3	45 minutes.
		4	35 minutes.
		5	15 minutes.
	Jesse Y. (hemophilic)	2	45 minutes.
		3	20 minutes.
		4	15 minutes.
		5	10 minutes.
	W. H. H. (normal)	2	20 minutes.
		3	10 minutes.
		4	10 minutes.
		5	5 minutes.
Nov. 16, 1912.....	Joseph Y. (hemophilic)	2	6 to 15 hours.
		3	3 to 6 hours.
		4	30 minutes.
		5	20 minutes.
	Jesse Y. (hemophilic)	2	6 to 15 hours.
		3	3 to 6 hours.
		4	30 minutes.
		5	20 minutes.
	D. R. H. (normal)	2	3 to 6 hours.
		3	30 minutes.
		4	15 to 20 minutes.
		5	10 minutes.
Dec. 21, 1912.....	Joseph Y. (hemophilic)	2	No clot in 24 hours.
		3	Begun in 1 hour.
		4	20 minutes.
		5	10 minutes.
	Jesse Y. (hemophilic)	2	No clot in 24 hours.
		3	Begun in 2 hours.
		4	20 minutes.
		5	15 minutes.
	H., hospital patient (normal)?	2	45 minutes.
		3	15 minutes.
		4	10 minutes.
		5	10 minutes.
	D. (normal)	2	No clot in 24 hours.
		3	?
		4	40 minutes.
		5	20 minutes.
Jan. 18, 1913.....	Joseph Y. (hemophilic)	2	No clot in 3 hours.
		3	15 minutes.
		4	10 minutes.
		5	5 minutes.
	Jesse Y. (hemophilic)	2	No clot in 3 hours.
		3	20 minutes.
		4	10 minutes.
		5	5 minutes.
	M. (normal)	2	1½ to 2 hours.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.

TABLE 1.—RESULTS OF EXAMINATION FOR ANTITHROMBIN IN HEMOPHILIC BLOOD.—(Continued.)

Date	Name	Thrombin in Drops	Time of Coagulation
April 19, 1913....	Joseph Y. (hemophilic)	2	20 to 25 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
	Jesse Y. (hemophilic)	2	20 to 25 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
	John S. (normal)	2	15 to 20 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
April 28, 1913....	Joseph Y. (hemophilic)	2	10 minutes.
		3	5 minutes.
		4	5 minutes.
		5	5 minutes.
	John S. (normal)	2	10 minutes.
		3	5 minutes.
		4	5 minutes.
		5	5 minutes.
May 17, 1913.....	Joseph Y. (hemophilic)	2	10 minutes.
		3	10 minutes.
		4	5 minutes.
		5	3 minutes.
	John S. (normal)	2	10 minutes.
		3	5 minutes.
		4	3 minutes.
		5	3 minutes.
March 26, 1913...	A. H. S. (hemophilic)	2	Small membrane at 25 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
	John S. (normal)	2	Small membrane at 20 minutes.
		3	5 minutes.
		4	5 minutes.
		5	5 minutes.
May 1, 1913.....	A. H. S. (hemophilic)	2	?
		3	15 minutes.
		4	10 minutes.
		5	5 minutes.
	George S. (normal)	2	?
		3	5 minutes.
		4	5 minutes.
		5	5 minutes.

PROTHROMBIN IN HEMOPHILIC BLOOD

The relative amounts of prothrombin in the hemophilic and normal bloods were determined by the simple method, described above, of first oxalating the blood and then adding the optimum amount of calcium chlorid to the clear plasma. This procedure was carried out on a great many specimens of blood, normal and pathological. It may be said in

general that the time of coagulation for normal human blood is quite constant, averaging about ten minutes, with variations from eight or nine to twelve or thirteen minutes. In normal dog's blood the time of coagulation is somewhat shorter, averaging about six minutes, with variations between five and nine or ten minutes. In the hemophilic bloods the results were entirely different, as shown by Table 2.

TABLE 2.—Results of Examination for Prothrombin in Hemophilic Blood

Date	Name	Calcium Chlorid, 0.5 Per Cent., in Drops	Time of Coagulation (5 Drops of Oxalated Plasma)
March 26, 1913...	A. H. S. (hemophilic)	1	No clot.
		2	90 minutes.
		3	120 to 150 minutes.
		4	120 to 150 minutes.
	John S. (normal)	1	No clot.
		2	9 minutes.
		3	12 minutes.
		4	14 minutes.
May 1, 1913.....	A. H. S. (hemophilic)	2	?
		3	Partly clotted in 3 hrs.
		4	Partly clotted in 3 hrs.
		5	?
	George S. (normal)	2	10 minutes.
		3	14 minutes.
		4	20 minutes.
		5	30 minutes.
April 19, 1913....	Joseph Y. (hemophilic)	2	No clot in 4 hours.
		3	No clot in 4 hours.
		4	No clot in 4 hours.
	Jesse Y. (hemophilic)	2	Clot in 2 to 2½ hours.
		3	Clot in 2 to 2½ hours.
		4	Clot in 2½ hours.
	John S. (normal)	2	10 minutes.
		3	12 minutes.
		4	18 minutes.
April 28, 1913....	Joseph Y. (hemophilic)	2	Clot later than 5 hours.
		3	Clot in 5 hours.
		4	Clot later than 5 hours.
	John S. (normal)	2	11 minutes.
		3	13 minutes.
		4	17 minutes.
May 17, 1913.....	Joseph Y. (hemophilic)	2	Clot in 3 hours to 3 hours, 10 minutes.
		3	Clot in 3 hours to 3 hours, 10 minutes.
		4	Clot later than 3½ hrs.
	John S. (normal)	2	8 minutes.
		3	10 minutes.
		4	12 minutes.

As will be seen from examination of the table, the optimum amount of calcium in the normal was obtained with two drops of the solution

of calcium chlorid. With this amount of calcium the clotting time of the normal plasma was, in the different experiments, 9, 10, 10, 11 and 8 minutes. The clotting time for the hemophilic bloods was 90, 180+, 240+, 120, 300, 180+ minutes.

The much delayed coagulation of hemophilic plasma under these conditions may be accounted for theoretically in several ways. It may be due, in the first place, to the presence of an excessive amount of antithrombin. The observations reported above give but little support to this explanation. The amount of antithrombin in hemophilic plasma may be somewhat greater than that found in normal blood, and according to my results, is never distinctly less than normal; but on the other hand, when it is present in normal amounts, the hemophilic blood still exhibits in a marked way the characteristic delay in coagulation when oxalated and again recalcified. In other words, there is no parallelism between the amount of antithrombin and the delay in coagulation, and we cannot therefore explain the latter phenomenon by reference to variations in the antithrombin. In the second place, the delayed coagulation of the hemophilic blood may be referred, as has been done by Sahli[9] and by Morawitz and Lossen, to a deficiency in thromboplastic substance, or rather to that particular form of thromboplastic substance which Morawitz has designated as thrombokinase. There is no satisfactory method of detecting variations in quantity of the thrombokinase. The authors named have arrived at the conclusion that thrombokinase is lacking in hemophilic blood (and hemophilic tissues), mainly by a process of exclusion of other possible explanations. I believe, and have given experimental reasons for the belief, that such a thing as thrombokinase does not exist. Morawitz's ingenious and attractive hypothesis in regard to this substance has proved to be an obstacle rather than an assistance in the study of the phenomenon of clotting. The reasons given for the existence of a kinase in the intestine with the property of activating trypsin, are convincing, since much in the way of direct proof is easily obtained. Any one may demonstrate that the mucous membrane of the intestine contains an organic substance which effects the rapid activation of trypsin. But no such proof is obtainable for the existence of a thrombokinase. From an experimental standpoint the whole matter is complicated here by the additional hypothesis that the kinase alone cannot activate thrombin, but requires the coactivity of calcium. That calcium is concerned in the activation of prothrombin to thrombin is beyond question, but every proof furnished to demonstrate that calcium alone is concerned in this activation is met by the objection that the kinase also is present in the solutions. Since this kinase has no known properties or reactions except that of assisting calcium in the activation

9. Sahli: Deutsch. Archiv. f. klin. Med., 1910, xcix, 518.

of thrombin, the argument assumes the form of a perfect circle. Kinase is necessary to the formation of thrombin, hence if thrombin is formed a kinase is present. What is usually designated as a thrombokinase in the blood and other tissues is in reality the substance or substances which facilitate the process of clotting, and which have long been known under the terms zymoplastic or thromboplastic substances. According to my work, they consist essentially of a special phosphatid (kephalin?), which accelerates the process of clotting, not by any direct action on prothrombin, after the manner of a kinase, but by its neutralizing effect on the antithrombin. In the general sense of the term it is a thromboplastic substance, but not a thrombokinase. Whether or not this material is lacking in hemophilic plasma, I have not been able to determine in any wholly satisfactory way. Addis[3] reports certain experiments which he believes demonstrate that as regards this factor there is no difference between normal and hemophilic plasma, but his experiments do not seem to me to be conclusive. Sahli, on the other hand, reports experiments on the thromboplastic effect of washed blood corpuscles from normal and from hemophilic blood, which seem to show that the former contain more thromboplastic material than the latter. But this conclusion, if correct, is scarcely applicable to the case under discussion. The thromboplastic substance liberated in the blood after shedding comes, it is assumed usually, from the disintegration of the platelets. When blood is received at once into oxalate solutions, this disintegration is prevented. The platelets are fixed, indeed, permanently fixed. When the blood is centrifugalized they are thrown down unchanged, as may be shown by microscopic examination, and subsequent treatment with water or saline solutions shows that they now possess a rigidity altogether different from their original condition in the normal plasma. It is probable, therefore, that when the normal or hemophilic blood is oxalated immediately and centrifugalized, the clear plasma obtained has not received an accession of thromboplastic substance from disintegrating platelets. Nevertheless under these conditions, addition of calcium to such plasmas is followed by prompt and uniform clotting in the normal plasma and by a much delayed and variable clotting time in the hemophilic plasma. My own explanation of the cause of this difference is similar to that proposed by Addis, namely, that the trouble lies in a variation in the prothrombin. This view is discussed further in the succeeding paragraph. Outside of all theoretical considerations, it is well to emphasize the fact that the simple procedure described above, of oxalating plasma and then recalcifying by adding calcium chlorid, gives a convenient method of detecting hemophilic blood and of distinguishing it from the bloods of other hemorrhagic conditions.

THE CAUSE OF HEMOPHILIA

In the recent admirable monograph on hemophilia by Bulloch and Fildes,[10] the condition is defined as "an inherited tendency in males to bleed." The definition is unsatisfactory, in that it fails to suggest a cause for the condition, and possibly also in that it lays too much stress on the hereditary feature. There is no question, of course, that hemophilia is transmissible by heredity, and that most of the undoubted cases reported exhibit this history, but on the other hand it cannot be denied at present that cases may arise spontaneously. To exclude such cases from the group of hemophilia because there is no evidence of a similar condition in the family records, is not justifiable. In all probability such spontaneous cases may in turn be transmitted according to the law controlling this inheritance. Outside its transmissibility as a sex-limited inheritance, hemophilia is characterized clearly by certain reactions or properties of the blood which distinguish it from other hemorrhagic conditions in which there is also a "tendency to bleed." The main distinguishing feature of the hemophilic condition is the greatly delayed coagulation time of the blood, when the blood is removed from the vessels without coming in contact with the tissues. This peculiarity is demonstrated more easily and certainly, in contrast with other bloods, if the specimen of blood is first oxalated, then centrifugalized to obtain a clear plasma and then recalcified by the addition of a suitable amount of calcium chlorid. If the specimen so treated should show a coagulation time exceeding that of the normal blood (nine to twelve minutes), there would be reason for claiming the presence of a hemophilic condition, and the gravity of the condition would be in proportion to the length of time required for coagulation.

All recent workers agree on this delayed or deficient coagulability as the characteristic feature of hemophilia and attempts to explain the proximate or ultimate cause of the condition start from this point. The nature of the explanations offered varies of course with the theory of coagulation adopted. Morawitz and Lossen and Sahli, adopting the theory of coagulation proposed by Morawitz, have been led to believe that the defect of the hemophilic blood consists in a deficiency or lack of thrombokinase; Weil[11] has suggested that the delayed coagulation may be caused by the presence of some inhibiting body (antithrombin); Wright[12] has attributed the trouble, in part at least, to a deficiency in calcium; Nolf, in accordance with his special theory of coagulation, supposes that there is a quantitative or qualitative defect in the factor of coagulation designated by him as thrombozym. Addis in his series of

10. Bulloch and Fildes: Hemophilia, Eugenic Laboratory Memoirs, University of London, 1911, xii.

11. Weil: Presse méd., 1905, p. 672; Bull. et mem. Soc. méd. d. hôp. de Paris, Oct. 26, 1906.

12. Wright: Brit. Med. Jour., 1893, p. 223.

thoughtful experiments has come to the conclusion that the essential difficulty lies in a change in the properties of the prothrombin. My own work has convinced me that the antithrombin theory of hemophilia is incorrect, in spite of the fact that my experiments were begun in the expectation of supporting this view. There is little or no positive evidence in favor of the view that a deficiency of calcium is the fundamental trouble, and I am persuaded that the explanations offered by Morawitz, Sahli and Nolf have been influenced by an incorrect theory of the process of clotting. Sahli's generalization that in the hemophilic there is a loss of thromboplastic power (thrombokinase), not only in the corpuscles of the blood, but in the tissues at large, is certainly not applicable in all cases. The slow clotting hemophilic blood may coagulate quite promptly if it is brought into contact with the tissue juices of the external tissues. There are at present, so it seems to me, no positive facts supporting this general view of a defect in thromboplastic material in the hemophilic blood. My own experiments have led me to believe that the trouble lies, where it was traced by Addis, in the factor of prothrombin; that is to say, the material from which the thrombin is formed. The experiments described above on the coagulation time of oxalated blood after the addition of calcium can only mean that this prothrombin material is deficient in quantity or altered in character. Addis has adopted the latter view. He believes that the prothrombin of the hemophilic blood is present in normal amounts, but is so altered in properties as to require a longer time than normal for activation to thrombin. This explanation has seemed to me to be improbable, because, in the first place, I have found, as reported in this paper, that addition of thromboplastic (phosphatid) material accelerates greatly the time of clotting of the hemophilic blood. Addis admits this fact, but claims that it is true only when large amounts of this material are used. Assuming that this latter qualification is correct, it does not affect the main conclusion that the prothrombin possesses its normal properties in relation to activation by calcium, since the thromboplastic material is effective only by virtue of the fact that it removes the antagonistic influence of the antithrombin. However, the point that Addis raises can be settled only by isolating the prothrombin from the hemophilic plasma and testing the action of calcium on it in comparison with prothrombin obtained by the same method from normal blood.

I have been able, fortunately, to obtain the prothrombin from blood plasma by the simple method which I have employed already for the isolation of thrombin. The method is as follows: Blood is obtained from a vein of the arm by means of a syringe and is oxalated at once (8 c.c. of blood to 1 c.c. of a 1 per cent. solution of sodium oxalate made up in sodium chlorid solution 0.9 per cent.). The specimen is centrifugalized and the clear plasma is drawn off. To this plasma is added an equal

volume of acetone and the precipitate is filtered off through a small filter. The filter paper is opened, the precipitate is spread to a thin layer and is then dried rapidly in a current of air from an electric fan. The dried filter paper with its adherent precipitate is cut into small pieces and is covered with water (8 or 10 c.c.) and allowed to stand for about half an hour. The extract is then filtered. The opalescent solution contains prothrombin, as can be shown most satisfactorily by its reaction with fibrinogen solutions. The fibrinogen solutions used for this purpose I have prepared from the plasma of cat's blood by a modification[13] of Hammarsten's method of repeated precipitation by half saturation with sodium chlorid. If the fibrinogen is precipitated three times the final solution in 0.9 per cent. sodium chlorid (with a trace of sodium bicarbonate if necessary) gives no coagulation at all on the addition of calcium, but clots readily with thrombin. With such solutions of fibrinogen, or indeed with the less pure solutions obtained by one or two precipitations, the presence of prothrombin in the solutions described above may be demonstrated very readily by experiments, of which the following is an example:

1. Fibrinogen solution, 10 drops + $CaCl_2$, ½ per cent., 1 drop = no clot in twenty-four hours.

2. Fibrinogen solution, 10 drops + prothrombin solution 3 drops = no clot in twenty-four hours.

3. Fibrinogen solution 10 drops + prothrombin solution 3 drops + $CaCl_2$, ½ per cent., 1 drop = clot in 2 to 3 minutes.

It should be stated that fibrinogen solutions prepared as described are not constant in their reactions. In some cases they clot very readily with thrombin; in other cases the clotting requires a longer time, and on standing for twenty-four hours or more the fibrinogen may undergo a modification of some kind so that it loses the property of yielding a clot on the addition of thrombin. In all cases, however, the freshly prepared fibrinogen may be used to demonstrate the presence of the prothrombin, since the solutions of the latter have no effect on the fibrinogen until calcium is added, and then the thrombic action is clearly shown. In order to determine whether or not the prothrombin from the hemophilic blood differs in its reaction to calcium from that of normal blood, I have prepared the prothrombin from one of the hemophilic subjects used in this investigation (Joseph Y.) and compared it with the prothrombin from a normal blood. The following results were obtained:

Experiment, Oct. 19, 1913.—Eight cubic centimeters of blood taken from Joseph Y. and 8 c.c. from a normal (John S.). Each specimen was oxalated and treated with acetone as described above. The aqueous solutions of prothrombin were tested on a freshly prepared fibrinogen solution.

Control Experiments.—Fibrinogen solution, 10 drops + water 5 drops + $CaCl_2$ (½ per cent.) 1 drop = no clot in twenty-four hours.

Fibrinogen solution, 10 drops + prothrombin solution 5 drops = no clot in twenty-four hours.

13. Howell: Am. Jour. Physiol., 1910, xxvi, 461.

Prothrombin from Normal Blood.—Fibrinogen solution 10 drops + prothrombin solution 5 drops + $CaCl_2$, 1 drop = clot in twenty-eight minutes.

Fibrinogen solution 10 drops + prothrombin 3 drops + $CaCl_2$, 1 drop = clot in 50 to 60 minutes.

Prothrombin from Hemophilic Blood.—Fibrinogen solution 10 drops + prothrombin solution 5 drops + $CaCl_2$, 1 drop = clot in twenty minutes.

Fibrinogen solution 10 drops + prothrombin solution 3 drops + $CaCl_2$, 1 drop = clot in fifty minutes.

This experiment, which was repeated several times with similar results, demonstrates quite definitely that the separated prothrombin from hemophilic blood yields active thrombin in the presence of calcium quite as readily as the prothrombin from normal blood. The qualitative difference claimed by Addis does not exist. In explaining the delayed coagulation of the hemophilic blood we must assume, it seems to me, that the prothrombin is present in subnormal amount in the circulating blood. Since the antithrombin, on the contrary, exists in normal or even in sligthly supranormal amounts, the delay in coagulation of the shed blood is readily explained. On the basis of the facts presented in this paper, I would conclude that the essential condition in hemophilic blood which is immediately responsible for its delayed coagulation is a subnormal amount of prothrombin in the circulating blood.

Hemophilia may be defined as a condition, limited to the male, in which the coagulation time of the blood is markedly prolonged in consequence of a deficiency in the amount of the contained prothrombin, with the additional characteristic that the defect is transmissible by heredity in accordance with the so-called law of Nasse.

The ultimate cause of this condition cannot be stated. So far as we know, the prothrombin present in blood-plasma is furnished by the blood-platelets, and it is reasonable to assume that the defect in question is referable to some functional change in these elements.

THROMBOSIS

During the course of this work the opportunity has offered to examine several cases of thrombosis in which there were no obvious mechanical or inflammatory conditions to account for the trouble. The cases are few in number, and unfortunately the examination was not complete in each case, but the results seem to be suggestive.

Case 4.—Dr. H., just recovering from mild attack of thrombosis involving the saphenous and the abdominal veins. Some soreness and edema over region involved. He had had several similar attacks at intervals of some weeks. Specimen of 8 c.c. of blood taken from an arm vein and compared with similar specimen from a laboratory attendant (John S.).

The results of this test indicate that the blood of the thrombotic patient contained less antithrombin than the normal with which it was compared, and, indeed, less than any of the normals used in any of these experiments.

Coagulation time (4 c.c.): Patient, 29 to 30 minutes.
Normal, 38 to 39 minutes.

ANTITHROMBIN TEST

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibr. Sol. Drops	Coagulation Minutes
		Normal.		
1	2	15	10	40
1	3	15	10	10
1	4	15	10	5
1	5	15	10	5
		Patient.		
1	2	15	10	10
1	3	15	10	5
1	4	15	10	5
1	5	15	10	5

CASE 5.—Charles G., patient in the Johns Hospkins Hospital, service of Dr. Barker. Aged 52. Onset of attack one month previous to admission; dyspnea on exertion, pain in left side, swelling of feet. Physical findings: dyspnea, hydrothorax, mitral and aortic insufficiency. Blood-pressure, 140. Blood-count, r. b. c., 4,300,000; w. b. c., 7,400; Hb., 90 per cent. The day before the blood was examined the patient developed a marked swelling of the whole left leg, diagnosed as due to thrombus in the left femoral or iliac vein. Some of the superficial veins at left elbow firmly thrombosed.

Specimen of blood, 10 c.c., taken from arm vein and compared with a similar specimen from one of the laboratory attendants (M.).

Coagulation time (2 c.c.): Patient, 8 minutes.
Normal, 41 minutes.

ANTITHROMBIN TEST

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibr. Sol. Drops	Coagulation Minutes
		Normal		
1	2	15	10	*
1	3	15	10	10†
1	4	15	10	5
1	5	15	10	5
		Patient.		
1	2	15	10	5
1	2	15	10	2
1	2	15	10	2
1	2	15	10	2

* First membrane at twenty minutes.
† Partial.

In this case also the amount of antithrombin was distinctly less than in the normal. In fact the clotting with the thrombotic plasma was so rapid as to indicate the practical absence of antithrombin in its heated plasma.

PROTHROMBIN TEST

Oxalated Plasma Drops	$CaCl_2$, ½ Per Cent. Drops	Coagulation Minutes
	Patient.	
5	2	7
5	3	7
5	4	9
5	5	11
	Normal.	
5	2	10
5	3	14
5	4	17
5	5	19

The more rapid clotting of the oxalated plasma of the thrombotic blood may have been due to a greater amount of prothrombin or to a

diminished amount of antithrombin. The previous test for antithrombin indicates that the latter explanation is probably the correct one, and this conclusion is borne out by a subsequent experiment in which the serum from the patient and from the normal were compared in regard to their strength in thrombin, the precaution being taken of adding to each an equal volume of kephalin-solution to neutralize the antithrombin present. This test gave the following result:

COMPARISON OF STRENGTH IN THROMBIN

Fibrinogen Solution Drops	Serum and Kephalin Drops	Coagulation Minutes
	Patient.	
10	2	12
10	3	6
10	4	5
10	5	3
	Normal.	
10	2	10
10	3	5
10	4	5
10	5	3

According to this test there was practically no difference in the amount of thrombin in the two specimens of serum.

CASE 6.—Mrs. N., private patient of Dr. Thayer. History of two attacks of thrombosis — one six years previously with evidence of thrombosed veins in calf, groin and inner side of leg, one beginning four months before examination and following attack of measles. There were pain and tenderness over left femoral vein, knots in groin and under skin of legs, first on left side, later on right side. In bed for three months. On one occasion when convalescing there was a sudden attack of severe pain in side, with marked dyspnea. A similar attack followed after an interval of some time. Examination of the blood was made four months after beginning of last attack when the patient had recovered and, showed no physical signs except slight edema in legs.

Coagulation time (2 c.c.): Mrs. N., 20 to 22 minutes.
Normal: Dr. D., 40 to 43 minutes.

PROTHROMBIN TEST

Five drops plasma + 2 drops $CaCl_2$ (½ per cent.) = clot in nine minutes.
Five drops plasma + 3 drops $CaCl_2$ (½ per cent.) = clot in twelve minutes.

ANTITHROMBIN TEST

This test was made with three dilutions of a new stock of thrombin. In two of these the concentration was too great, so that the tubes clotted more rapidly than was convenient for a decisive comparison. In each case, however, the clotting in the tubes containing the heated plasma from the patient preceded that in the controls, indicating, therefore, less antithrombin in the patient's blood. This difference was shown most distinctly with the third dilution of thrombin used as follows:

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibrinogen Drops	Coagulation Minutes
		Normal.		
1	3	15	10	15 to 20
		Patient.		
1	4	15	10	15 to 20
1	3	15	10	7
1	4	15	10	5

CASE 7.—In a fourth case of thrombosis examined the results were negative. This patient was a hospital nurse with a history of repeated attacks, diagnosed by Dr. Boggs as due to venous thrombosis. At the time of examination of her blood she had been free from any trouble for several months. The examination made was incomplete, including only the coagulation time, thirty-five minutes, and the prothrombin test, ten minutes. As these times were entirely normal the antithrombin tests were not made, owing to circumstances which could not be controlled. This examination was made May 31. Later in the summer the patient had another severe attack, but was not accessible for examination.

The number of cases reported is small, but the indications from the blood examinations of a diminution in antithrombin, especially in Case 2, are sufficiently positive to warrant a suspicion that herein may lie the important factor responsible for the formation of a thrombus. If the antithrombin constitutes a normal defensive agency against intravascular clotting, a diminution in this substance will bring about a condition in which spontaneous coagulation will be favored, particularly in those parts of the circulation in which the mechanical conditions are such as may lead to a partial stasis of the circulation.

In the hemophilic blood there seems to be a relative excess of antithrombin, owing mainly to an actual diminution in the amount of prothrombin. In the blood of patients showing spontaneous thrombosis, just the opposite condition prevails of a deficiency in antithrombin relative to the amount of prothrombin present.

SUMMARY

1. Methods are described for testing the relative amount of prothrombin and antithrombin in the blood.

2. The application of these methods to hemophilia shows that the blood in this condition is deficient in prothrombin. The antithrombin may be normal or somewhat greater than normal. The characteristic peculiarity of hemophilic blood is its markedly delayed time of coagulation. This peculiarity is explained by the diminution in amount of the prothrombin which results in a relative excess of antithrombin.

3. The detection of a hemophilic condition of the blood is facilitated by first oxalating the blood and then recalcifying with an optimum amount of calcium. Under these conditions the time of clotting exhibited by normal plasma is very constant (nine to twelve minutes). That of hemophilic blood is greatly delayed.

4. In patients suffering from spontaneous thrombosis of the veins there is evidence of a diminution in the antithrombin of the blood, the prothrombin being normal. It is suggested that this deficiency in antithrombin operates as a favoring, perhaps as a determining, factor in the production of the thrombus.

5. In purpura hemorrhagica and other forms of so-called purpura, no evidence was found of any variation from normal in either the antithrombin or the prothrombin.

A CLINICAL STUDY OF AMYLASE * IN THE URINE

WITH ESPECIAL REFERENCE TO THE PHENOLSULPHONEPHTHALEIN TEST†

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Since Majendie,[1] in 1846, first found an amylolytic enzyme in human blood, and later, in 1863, Cohnheim[2] wrote of its presence in the urine, Plósz and Tiegil,[3] Foster,[4] Lépine[5] and many other writers have confirmed these earlier investigators and attempted to determine the quantitative value of amylase with reference to certain pathological conditions, more particularly those of the kidney. All the various methods devised were unwieldy and inaccurate however, and most of the information gained contradictory. In 1908 Wohlgemuth[6] devised a quantitative test which for the simplicity, accuracy and uniformity of its results so far surpassed any test previously proposed that it has been generally adopted by chemists and clinicians alike for the estimation of amylase in blood, urine, feces and other body substances.

Nearly all the contributions to our literature on this subject have come from French and German writers, and in Germany particular attention has been directed to the quantitative estimation of amylase in blood and urine.

Wohlgemuth's original method devised for the quantitative estimation of amylase has been followed by numerous investigations into the experimental and clinical aspects of this ferment as found in the body fluids. The largest portion of this work has been done by Wohlgemuth and his pupils and has yielded very interesting results.

In order that we may have a clearer understanding of what is to follow, it seems advisable to give in detail the technic of Wohlgemuth's

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* Throughout this paper the term amylase has been used in preference to the term diastase so generally employed by German writers, amylase having a more restricted significance than diastase; "d" as a means of expressing the readings obtained is used simply in deference to the terminology employed in Wohlgemuth's original method.

† From the Blumenthal Fellowship Foundation of the Medical Clinic, College of Physicians and Surgeons, Columbia University.

†Submitted for publication, Aug. 1, 1913.

1. Wajendie: Compt. rend., Acad. d. sc., 1846, xxiii, 189.
2. Cohnheim: Virchow's Arch. f. path. anat., 1863, xxviii, 241.
3. Plósz and Tiegil: Arch. f. d. ges. Physiol. (Pflügers), 1873, vii, 391.
4. Foster, M.: Jour. Anat. and Physiol., 1867, i, 107.
5. Lépine: Compt. rend., Acad. d. sc., 1891, cxiii, 1014.
6. Wohlgemuth, J.: Biochem. Ztschr., 1908, ix, 1.

"starch-iodin" method for the quantitative estimation of amylase as outlined in his most recent publication on this subject.[7] This differs in a few details only from his original method, which may be found in any text-book on physiological chemistry.

TECHNIC

Ten test-tubes numbered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 are placed in a test-tube stand (these tubes must be thoroughly cleansed, rinsed in distilled water and carefully dried). To each tube is added 1 c.c. of a normal saline solution from a graduated pipet (except in Tube 1, which contains 1 c.c. of the fluid to be tested). With a 1 c.c. pipet, accurately graduated into 0.1 c.c., draw up 1 c.c. of fluid to be tested and add to Tube 2, thoroughly mixing the fluids by three times drawing up the mixture of normal saline solution and test fluid and again expelling contents into the tube. Then finally draw up 1 c.c. of the fluid now diluted 1 to 2 and place this in Tube 3, repeating the same process of mixing and again withdrawing 1 c.c. of mixture. This is to be repeated in all the succeeding tubes and in the last tube the 1 c.c. withdrawn can be discarded. This will give the following amounts of fluid to be tested in each tube (seven tubes suffice in most cases).

No. 1 = 1.0 c.c.; No. 2 = 0.5 c.c.; No. 3 = 0.25 c.c.; No. 4 = 0.125 c.c.; No. 5 = 0.0625 c.c.; No. 6 = 0.032 c.c.; No. 7 = 0.016 c.c.; No. 8 = 0.008 c.c.; No. 9 = 0.004 c.c.; No. 10 = 0.002 c.c.

Now to each tube are added 2 c.c. of 0.1 per cent. starch solution (Kahlbaum's soluble starch), the tubes fitted into a wire cage after shaking gently, the cage placed on a water-bath at 38 C. for half an hour. The temperature should be very carefully watched, should be kept within one-half degree of 38 C. and the time accurately measured. At the end of this time all tubes are withdrawn and placed in ice-water for five minutes to inhibit further amylolytic activity and are then replaced in test-tube stand. To each tube is then added 2 drops of fiftieth-normal iodin solution which must be freshly prepared from a stock solution of tenth-normal strength daily.[8] One-to-one-thousand starch solution should be freshly prepared every three days and kept in refrigerator.

READING

If the urine is normal the first two or three tubes will be golden yellow in color, all starch having been digested, while the fourth will be reddish with no tinge of blue, the fifth violet and the others blue.[9] The tube from which the reading is taken is the deep-red tube; this tube shows that all starch has been digested at least to the dextrin stage.

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7. Wohlegmuth, J., and Noguchi, Y.: Berl. klin. Wchnschr., 1912, xxiii, 1069.

8. In case 2 drops of iodin solution to each tube is not sufficient to bring out a permanent color, add as many more drops to the tube as will be necessary, being careful to add exactly the same number of drops to each of the other tubes.

9. The various gradations in color as given above are not always the same; in fact it may be difficult to determine in some instances which tube constitutes the end-point or reaction tube but after some practice, the eye becomes trained to recognize that tube which no longer contains a bluish tint. Corbett (Quart. Jour. Med., 1913, vi, 351) in a very recent publication emphasizes the "mauve tube" as the "limit" tube and calculates from the tube preceding this, (the one with a "reddish-yellow color.") Wohlgemuth (see Note 7) defines the end point as follows: "Dasjenige Gläschen, in welchem der erste blaue Farbenton auftritt, das also bei Zusatz von Jod rotblau wird, gilt als Grenze (Limes) der Wiksamkeit und aus der in dem vorhergehenden Gläschen enthaltenen Serummerge wird die Fermentstärke berechnet."

The calculation is then made as follows: In Tube 4 there was 0.125 c.c. urine or fluid which digested 2 c.c. of a 0.1 per cent. starch solution in half an hour at 38 C. Therefore 1 c.c. of fluid to be tested would digest starch according to the following equation:

$$0.125:2 \text{ c.c. (starch)} :: 1 \text{ c.c.} : X = 16$$

One c.c. of fluid digested 16 c.c. of a 0.1 per cent. starch solution in half an hour; this Wohlgemuth designates as follows:

$$\frac{38^\circ}{d\ 30'} = 16$$

When twenty-four-hour digestion is employed he expresses it:

$$\frac{38^\circ}{D\ 24\ hr.} = X.$$

The present work was undertaken with the object of determining two things: first, the clinical value of the estimation of amylase in the urine in determining the functionating powers of the kidney in various diseases, more particularly in renal and cardiac cases; second, the relationship between this test and another test of renal function, namely, the phenolsulphonephthalein test of Rowntree and Geraghty.

Most of the cases here reported fall under renal or cardiac headings, as these two conditions are the ones in which functional tests are most often made. But several other diseases have also been investigated with very interesting results. I had hoped also to make comparisons of the amylolytic value of the blood-serum synchronously with that of the urine, but, except in a few cases, this has not been possible, and will have to be taken up at some future date. In all cases investigated, samples of a twenty-four-hour specimen were used for reasons which will be explained later.[10]

The quantitative estimation of amylase in the urine as a test for the functional activity of the kidneys has been advanced by Wohlgemuth,[11] Benczur,[12] Wynhausen,[13] Rosenthal,[14] Marino,[15] Corbett[8] and Neuman.[16] Wohlgemuth[11] used it in conjunction with phloridzin, indigo-carmin and cryoscopy tests to determine unilateral disease of the kidney and found in a series of some fifty cases that it, with the freezing-point test, gave the most valuable results in estimating the relative functionating powers of the two kidneys. Wohlgemuth,[7] Corbett,[8] Neuman[16] and Rosenthal[14] have shown that the amount of amylase in the urine of normal individuals

10. A few cubic centimeters of toluol should be added to all twenty-four-hour specimens, to prevent bacterial growth. This does not interfere with the "d" readings, and preserves the urine for six months or more, giving the same "d" reading at the end of that time as when freshly voided.

11. Wohlgemuth, J.: Ztschr. f. Urol., 1911, i, 801.

12. Benczur, J.: Wien. klin. Wchnschr., 1910, xxiv, 890.

13. Wynhausen, O. J.: Berl. klin. Wchnschr., 1910, xlvi, 2107.

14. Rosenthal, A.: Deutsch. med. Wchnschr., 1911, xxxvii, 923.

15. Marino, E.: Deutsch. Arch. f. klin. Med., 1911, ciii, 325.

16. Neuman: Deutsch. Arch. f. klin. Med., 1913, cix, 164.

varied within very narrow limits, and for a given individual was almost constant, provided a twenty-four specimen was used. That there may be great variations in the amylolytic power of individual specimens of urine passed at certain times during the twenty-four hours, Wohlgemuth has shown as follows:[17] 1. There is more amylase in urine of fasting periods, that is, just before meals. 2. The amount begins to diminish after meals and gradually sinks until three or four hours after a meal, then gradually begins to rise again. This confirms the earlier investigations of Grützner,[18] Gehrig,[19] Hoffman,[20] Rosenberg[21] and Leo,[22] who worked with cruder methods.

It has also been shown by Wohlgemuth[23] by experiments on dogs that neither the kind nor amount of food taken has any effect on the quantity of amylase in the blood-serum. Schlesinger[24] found the same for man, while Corbett[8] concludes that in human beings the quantity of amylase in the twenty-four-hour urine does not vary even with marked dietary changes. He gives one instance, however, that of an infant aged 9 months, who had never had unaltered starch food before, and whose urine, after three days' administration of starch-containing food, showed an increase in amylolytic power amounting to almost five times as much as before the giving of starch. Neuman[16] also concludes that changes in diet have no effect on the quantity of amylase in urine.

The influence[17] of sex on the amount of amylase in the urine shows that the urine of males has a slightly higher "d" reading than that of females. This, however, is so small as to be negligible in clinical work.

According to Wohlgemuth,[17] Corbett,[8] Wynhauser[13] and Marino,[15] the reaction and salt concentration of the urine has no appreciable effect on the "d" readings. In this connection it may be mentioned that Cole,[25] working with a pure (dialyzed) solution of ptyalin, shows that the effect of any electrolyte on the rate of action of the ferment is dependent on two factors — first, the acceleration due to anions other than hydroxylions, and second, the depression due to kations and hydroxylions.

Wohlgemuth[26] himself, after careful studies of the salivary amylase, pancreatic amylase and the amylase of blood-serum, all of which he found to have the same properties, came to the following conclusions:

1. Sodium chlorid increases amylolytic action in twenty-four hours' digestion ten fold.

17. Wohlgemuth: Biochem. Ztschr., 1909, xxi, 432.
18. Grüttzner: Breslauer ärztl. Ztschr., 1882, xvii, 193.
19. Gehrig, J.: Arch. f. d. ges. Physiol. (Pflügers), 1885, xxxviii, 38.
20. Hoffman: Arch. f. d. ges. Physiol. (Pflügers), 1887, xli, 148.
21. Rosenberg: Dissertation, Tübingen, 1890.
22. Leo: Verhandl. d. VII. Kongr. f. inn. Med., 1888, 364.
23. Wohlgemuth, J.: Biochem. Ztschr., 1909, xxi, 381.
24. Schlesinger, W.: Deutsch. med. Wchnschr., 1908, xiv, 593.
25. Cole: Jour. Physiol., 1904, xxx, 202.
26. Wohlgemuth, J.: Biochem. Ztschr., 1908, ix, 10.

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2. The lowest dilution in which sodium chlorid seemed to have an accelerating action was 0.002 to 0.00097 per cent.

3. The increased effect of sodium chlorid is due to the anion chlorid, therefore all other chlorid-containing neutral salts accelerate the enzyme.

4. Of the other halogen ions bromin also increases the action; also iodin, but to a less degree, while fluorin inhibits.

5. Alkalies, except sodium carbonate, inhibit the action of amylase and destroy it by prolonged action.

6. Neutral salts like sodium phosphate, oxalate and acetate inhibit the action of amylase, whereas the nitrate, nitrite and chlorate increase the action. Sodium sulphate is indifferent.

7. Alanin and leucin inhibit, glycocol is indifferent.

8. Colloid metals (gold, silver, copper and iron), inhibit in proportionately smaller concentration, while in strong dilution they are indifferent and the addition of sodium chlorid does not alter their behavior.

As the amylase in urine is probably derived directly from that of the blood it must have the same properties as that of the blood. It can, therefore, readily be seen how difficult it would be to determine the individual factors concerned in the composite action of the various ions on the amylolytic power in such an ion complex as the urine. Of the urines I have studied, some two hundred in number, I have had only two, and both were from the same patient, which showed an alakine reaction; all the others were neutral or acid, the majority being acid. No appreciable effect on the "d" readings caused by reaction could be noted, except when decomposition was evident, this seeming to accelerate the action of amylase.

Other factors affecting action of the ferment in urine must here be mentioned. First, the action of blood. It has been shown[27, 28] that blood and various organ extracts have a marked accelerating action on the amylolytic activity of pancreatic juice, saliva, etc. So that urine containing blood will show a much higher amylolytic power than normal urine. Dudley Corbett,[8] in a very recent publication has also demonstrated that the influence of blood on the amylolytic action of the urine is a strongly accelerating one. Neuman,[16] however, states that in "several cases" during menstruation no effect could be noted. He does not state definitely, however, how much blood was present nor does he say whether the specimens examined were complete twenty-four-hour ones. Both these factors are important, particularly the former, as I have often centrifuged specimens of urine from menstruating women and in the sediment found only small numbers of red blood-cells, absolutely no macroscopic evidence of blood being present. It is only reasonable to

27. Wohlgemuth, J.: Biochem. Ztschr., 1911, xxxiii, 303.
28. Pozerski, L.: Thèse de Paris, 1902, 70.

suppose that in these cases when such relatively minute quantities of blood were present, no, or very slight, alteration in the "d" value would be found.

Another factor which must be considered in regard to its effect on amylolytic activity in the urine is albumin. Very few authors have dealt with this at all. Lüthje[29] found high amylase value in albuminous urines. Rosenthal[14] found that the chronic interstitial forms of nephritis showed uniformly lower readings that did other forms, and generally less albumin is found in the chronic interstitial forms. He draws no deductions, however. Benczur concludes that high "d" readings are sometimes found in nephritics and other albuminuric conditions. He argues that his and Wohlgemuth's experiments[30] in which they found increased "d" value for blood-free kidney extracts of diabetic animals, show that the kidney plays some part in the production of urinary amylase, and further, that the inflammatory condition which produces albuminuria may also serve to stimulate the kidney cells to increased amylase production. Neuman[16] denies any influence on the part of albumin or pus. Corbett, whose series of cases is small, gives this subject more detailed attention and theorizes as follows: The damage of kidney structure may be equally severe in cases with little or much albumin. The presence of much albumin is attributed to increased permeability of the kidney and the high "d" values so often obtained in these cases are due to the same factor. "For," he argues, "if the renal cells are permeable to the complex protein mixture, generally termed albumin, they should the more readily allow the passage of a simpler colloid, such as amylase." To support this theory he refers to cases of eclampsia with much albumin and many casts in which the "d" values were very high and in which there must have been severe damage to kidney structure. All the clinical evidence to date certainly points to higher "d" values in those forms of nephritis with high albumin content of the urine than in those forms with little or no albumin which almost invariably give low readings for "d."

In stating the results in my own series of cases I have adopted a purely arbitrary method in comparing the amounts of albumin found in different cases; for instance, anything tabulated as trace or faint trace is designated as "little albumin," while anything from heavy trace to much albumin or a definite quantitative figure is designated as "much albumin."

On examination of the figures in Table 1 with reference to the influence of albumin on the "d" reading, thirty-four cases[31] are found which have varying degrees of albuminuria; twelve cases which have

29. Lüthje, H.: Festschr. f. J. Rosenthal, 1906, ii, 131-138.

30. Wohlgemuth, J., and Benczur: Biochem. Ztschr., 1909, xxi, 460.

31. Case 29 is omitted as here the pus was very large in amount and was probably the main source of the albumin.

TABLE 1.—CHRONIC INTERSTITIAL NEPHRITIS.

Case	Name	Sex	Date	Amylase	Urine				
					Quant. c.c.	Sp. Gr.	Albumin	Casts	Blood
1	D. W.	M.	10/31/12	8	1,770	1,008	Tr.	Many hyal. and gran.	Occ. R. B. C.
			1/15/13	2	1,200	1,015	H. Tr.		
			3/ 6/13	4	2,020	1.020			
			3/13/13	4	1,500	1.009			
			3/22/13	8	1,200	1.015	H. Tr.		
2	L. K.	F.	10/31/12	4	850	1.020	H. Tr.	Many hyal. and gran.	0
3	E. H.	F.	10/31/12	2	1,230	1.012	V. F. Tr.	Few	0
4	A. P.	F.	10/31/12	8	900	1.018	Much	Waxy gran., hyal.	Few R. B. C.
5	J. K.	M.	11/ 3/12	2	1,830	1.027	F. Tr.	Hyal., gran.	Few R. B. C.
6	M. R.	M.	11/ 3/12	4	1,500	1.020	V. H. Tr.	Gran., waxy hyal.	Few R. B. C.
7	A. W.	M.	11/27/12	2	1,620	1,008	F. Tr.	Hyal., gran.	0
			12/20/12	0	1,740	1.006			
			2/ 1/13	2	1,560	1.010			
8	G. D.	M.	11/ 2/12	0	930	1.019	V. F. Tr.	Hyal., gran. (many)	Few R. B. C. once.
			12/16/12	16	1,830	1.013			
			5/11/13	2	2,040	1.012			
9	S. D.	F.	12/22/12	4	1,400	1.012	F. Tr.	Occ. hyal., gran.	Few R. B. C.
			1/ 9/13	4	1,300	.....			
			2/ 1/13	4	1,365	.....			
10	M. R.	M.	1/10/13	2	2,075	.....	V. F. Tr.	0	0
			1/22/13	4	790	1.020			
			2/ 3/13	2	790	1.030			
			2/14/13	4	1,230	.....			
11	J. S.	F.	1/10/13	4	1,100	.....	V. F. Tr.	0	Occ. R. B. C.
			1/16/13	0	1,630	1.012			
			1/23/13	4	1,280	.....			
			1/26/13	4	730	1.016			
			1/28/13	4	1,450	.....			
12	G. H.	M.	1/15/13	32	1,050	.....	H. Tr.	Gran., hyal.	0
13	F. R.	M.	1/18/13	2	1,200	.....	H. Tr.	Gran., hyal.	0
			2/26/13	2	1,760	.....	F. Tr.		
14	R. P.	F.	1/18/13	4	1,800	.....	V. F. Tr. (Sugar)	0	R. B. C. few.
15	C. M.	M.	1/26/13	2	2,700	.....	H. Tr.	Many hyal., gran.	Many R. B. C.
			1/31/13	2	2,400	.....			
			2/14/13	2	1,400	.....			
16	M. S.	F.	2/ 3/13	8	2,705	1,036	H. Tr.	Hyal., gran.	0
17	J. T.	M.	1/21/13	2	630	.....	V. H. Tr.	Gran. hyal.	R. B. C. Many for two days after operation.
			2/ 4/13	8	995	.....			
			2/ 6/13	16	750	.....			
			2/12/13	32	630	.....			
			2/13/13	31	660	.....	2%		
			2/15/13	32	1,040	.....			
			2/21/13	32	1,000	.....			
			2/26/13	32	950	.....	V. H. Tr.		
			3/ 6/13	8	1,500	.....			
			3/13/13	16	930	.....			
			3/17/13	32	700	.....			
			3/19/13	32	900	.....			
			5/ 8/13	32	1,350	.....			

Urine			Date	Disease	Result
Blood Pressure	Reaction	Phenol-sulphone-phthalein Per Cent.			
240 (S) to 80 (S) (term).	Acid	55 45 56	10/27/12 11/13/12 3/ 5/13	Chronic interstitial nephritis.	Died
170 (S) to 200 (S)	Acid	45	10/26/12	Chronic interstitial nephritis. This patient had hyperglycemia and persistent glycosuria. Regarded as a case of dyspituitarism.	Improved
205 (S)	Acid	26	10/ 3/12	Chronic interstitial nephritis.	Improved
130 (S)	Acid	None made.	.....	Chronic par. neph. (Some edema. Chronic pul. tuberculosis. Always fever.)	Died
.....	Acid	F. Tr.	11/ 2/12	Chronic interstitial nephritis. (Atony of bladder.)	Improved
130 (S) 80 (S)	Acid	36	11/ 2/12	Had marked amyloid change in kidney, liver and spleen at necropsy.	Died
220 (S) 250 (S)	Acid	Less than 5 Trace 1 1	11/22/12 12/ 3/12 1/ 6/13 1/15/13	Chronic interstitial nephritis. (Necropsy showed extreme art. scl. of bl. ves., kidney, etc.)	Died
180 (S) to 200 (S)	Acid	13	11/ 4/12	Chronic interstitial nephritis. (Empyema of frontal sinus, secondary diagnosis.)	Died
.....	Acid	10 5 3	12/ 6/12 1/ 6/13 2/ 3/13	Chronic interstitial nephritis. (Secondary anemia.)	Improved
Within normal limits	Acid	32 38	1/ 9/13 1/21/13	Chronic interstitial nephritis. (Chronic card. valv. dis.)	Improved
200 (S)	Acid	16 10	1/ 9/13 1/24/13	Chronic interstitial nephritis. Congenital cystic kidney and hydrothorax.	Improved
200 (S)	Acid	33	1/14/13	Chronic interstitial nephritis.	Died
220 (S)	Acid	5 Trace	1/16/13 11/25/13	Chronic interstitial nephritis.	Improved
170 (S)	Acid	57	1/16/13	Chronic interstitial nephritis. (Diabetes not severe but may be primary disease.)	Improved
180 (S)	Acid	11 76	1/25/12 2/13/13	Chronic interstitial nephritis. (Acute tonsillitis.)	Improved
.....	Acid	48	2/19/13	Chronic interstitial nephritis. (Acute cardiac dilatation.)	Improved
190 (S)	Acid	40 23 13 16 10 13 31 29 66 60 46 44	10/16/12 11/12/12 12/10/12 12/23/12 1/10/13 1/27/13 2/10/13 2/25/13 4/ 2/13 4/21/13 5/ 6/13 5/24/13	Chronic parenchy. nephritis. Jan. 30, 1913, had double decapsulation of kidneys. Since then edema has disappeared. Developed symptoms since Feb. 19, 1913, of pul. tuberculosis with fever. Discharged July 8, 1913. Still fever.	Improved

TABLE 1.—CHRONIC INTERSTITIAL NEPHRITIS.

Case	Name	Sex	Date	Amlase	Urine				
					Quant. c.c.	Sp. Gr.	Albumin	Casts	Blood
18	M. B.	F.	2/ 6/13	16	1.355	1.016	H. Tr.	Gran.,	0
			2/ 8/13	16	1,200	1.022		hyal.	
19	E. J.	F.	2/ 4/13	2	1,150	1.010	V. H.	Very	0
			2/ 5/13	2	1,400	.....	Tr.	many waxy	
			2/12/13	0	1,160	.....	0.2%	hyal., gran.	
			2/21/13	0	1,000	.....	to		
			3/ 6/13	0	1,005	.....	1%		
			3/13/13	0	900	.....			
			3/16/13	0	520	.....			
20	C. W.	F.	2/ 9/13	2	1,530	.....	H. Tr.	Hyal.	Few
			2/10/13	2	1,470	.....			R. B. C.
			2/21/13	2	1,010	.....			
21	K. D.	F.	2/ 9/13	8	2,100	1.023	V. H.	Hyal.,	Much
			2/10/13	8	1,120	1.017	Tr.	gran.	blood.
22	J. M.	M.	2/14/13	16	1,170	.....	V. H.	Hyal.,	0
			2/16/13	16	1,020	.....	Tr.	gran.	
23	C. S.	M.	2/19/13	8	520	1.025	V. H.	Hyal.,	Many
							Tr.	gran.	R. B. C.
24	B. G.	F.	2/ 8/13	4	255+	.....	Tr.	0	Few
									R. B. C.
25	N. F.	M.	3/ 6/13	8	1,350	1.010	V. H.	Hyal.,	Few
			3/11/13	0	1,950	1.016	Tr.	gran.	R. B. C.
			3/12/13	8	1,800	.....	Tr.	(many)	
			3/13/13	8	1,260	.....	V. H. Tr.		
			3/17/13	0	1,520	.....			
26	J. F. G.	M.	3/ 7/13	8	1,500	1.012	H. Tr.	Hyal.,	0
			3/12/13	8	1,450	1.020		gran.	
			3/18/13	16	700	.....		(many)	
27	S. M.	F.	3/12/13	0	950	.....	3%	Hyal.,	Few
			3/18/13	0	700	.....		gran.	R. B. C.
28	P. C.	M.	3/22/13	0	1,170	.....	Tr.	Hyal.,	0
								gran.	
29	C. M.	M.	4/ 9/13	2	1,800	1.010	H. Tr.	Hyal.	R. B. C.
			4/12/13	0	1,870	.....			much pus.
			4/16/13	2	2,240	1.022			
30	D. C.	M.	3/ 4/13	4	1,480	1.015	V. H.	Hyal.,	R. B. C.
							Tr.	gran.	few.
31	R. C.	M.	5/14/13	4	900	1.013	H. Tr.	Hyal.,	0
								gran.	
32	S. C.	M.	5/ 1/13	4	1,250	.....	Tr.	Hyal.,	R. B. C.
			5/15/13	4	1,500	.....		gran.	few.
33	J. Y.	M.	5/22/13	2	1,500	.....	H. Tr.	Hyal.,	R. B. C.
			6/15/13	2	1,200	.....		gran.	many
34	J. M.	M.	5/15/13	2	1,400	1.015	H. Tr.	Hyal.,	R. B. C.
								gran.	many.
								and fatty.	
35	T. V.	M.	1/25/13	8	905	1.019	Tr.	Hyal.,	0
								gran.	

CHRONIC PARENCHYMATOUS NEPHRITIS—(Continued)

Urine			Date	Disease	Result
Blood Pressure	Reaction	Phenol-sulphone-phthalein Per Cent.			
210 (S)	Acid	33 69	2/ 7/13 3/10/13	Chronic interstitial nephritis. (Chr. card. valv. dis.)	
130 (S) 160 (S)	Acid	3 11 10	1/ 6/13 1/27/13 2/ 3/13	Chronic interstitial nephritis. Necropsy: Chronic dif. neph. (amyloid.) Aortic and mitral endocarditis. (Regurgitation and stenosis.)	Improved
.....	Neutral	F. Tr. F. Tr.	1/ 3/13 2/14/13	Chronic interstitial nephritis.	Unimproved
180 (S)	Neutral	58	2/ 7/13	Chronic interstitial nephritis.	Improved
215 (S)	Acid	35	2/13/13	Chronic interstitial nephritis.	Improved
200 (S)	Acid	53	.....	Chronic interstitial nephritis. Cardiac hypertrophy. Tabes dor.	Improved
240 (S)	Acid	28 65	2/17/13 3/ 5/13	Necropsy: Chronic dif. neph. Hemorrhage into cerebrum.	Died
Above 160 (S)	Acid	12 19	3/ 4/13 3/ 8/13	Chronic interstitial nephritis.	Improved
.....	Acid	44 42	3/10/13 3/22/13	Chronic interstitial nephritis.	Improved
.....	Neutral	None made.	.....	Chronic par. nephritis.	Improved
150 (S)	Acid	13	4/19/13	Acute nephritis; bronchitis.	Cured
.....	Acid	Trace Trace Trace	4/ 8/13 4/15/13 5/12/13	Pyelitis (bilateral). Uremia. Delayed excretion urine, bloody, from left ureter.	Died
.....	Acid	28	4/27/13	Chronic parenchymatous neph.	Improved
.....	Acid	15	5/ 9/13	Chronic interstitial nephritis.	Died
.....	Acid	52	3/ 7/13	Chronic interstitial nephritis.	Improved
180 (S)	Acid	5 Trace	5/20/13 6/13/13	Chronic interstitial nephritis.	Died
.....	Acid	24 16	5/13/13 6/13/13	Chronic interstitial nephritis. (Chr. card. valv. dis.)	Died
140 (S)	Acid	70 54	1/13/13 1/23/13	Chronic interstitial nephritis.	Died

"little albumin" give subnormal "d" readings; eleven cases which have "much albumin" give subnormal "d" readings, Case 12 showing both; seven cases which have "much albumin" give normal or high normal "d" readings; while two cases in which there was little albumin give low normal "d" readings, and both these cases give normal phthaleins.

Cases 1, 17 and 25 do not permit of classification as regards this subject, as all have shown much albumin with varying "d" readings.

No hard-and-fast conclusions can be drawn from these figures, both because the method of estimating the quantity of albumin is purely an arbitrary one, and because the number of cases is not sufficient, but the results are at least suggestive of the fact as observed by other investigators that in cases of nephritis with high albumin content there is a greater tendency to normal or high normal "d" values than in those with small albumin content, when the "d" readings are almost invariably subnormal, and further, in those urines, when in spite of a high albumin content, persistently subnormal "d" readings are found, it can be assumed that the functional damage has been all the more severe. In all cases we must not forget the possible effect of blood if that be present. Also the presence of pus of extra-renal origin as a factor in the production or intensification of the albumin test must not be overlooked, in view of what Neuman[16] asserts, that is, that pus has no influence on the "d" readings.[32]

The question of dilution and its effect on the quantitative estimation of amylase is one that has been the subject of much discussion on the part of many observers. Wynhausen,[13] Marino,[15] Corbett,[8] Rosenthal[14] and Benczur[12] argue that its influence is a very limited one, and in the range of normal twenty-four-hour urines no appreciable effect is noted on the "d" readings. Wynhausen[13] quoted a case in which two readings were identical in the case of a patient who had 700 c.c. of urine, specific gravity 1.015, and a month later had 2,500 c.c. of urine, specific gravity 1.015. All the other authors mentioned above quote many similar cases. They agree that only in cases of extreme variations in amount do the "d" values change. One of my patients who had shown a reading of 32 on two occasions, only five days apart, with urine quantity amounting to 940 c.c. and 1,300 c.c., showed fifteen days later a reading of 8, with a urine quantity of 4,000 c.c. This was a patient who had an exophthalmic goiter (Case 10, Table 3), whose condition throughout her stay changed very little. In each instance the "d" reading was within normal limits, although the effect of the diuresis on the last "d" reading can readily be seen. Extremely low amounts of urine (under 500) are found only, as

32. Neuman's work appeared after this investigation had been concluded and the tables made out. Allusions to his work have been included only as they could be added to the text and had reference to what has already been written. His work on the effect of dilution on the "d" reading has not been alluded to as no time to study its application has been available.

a rule, in renal and cardiac condition, and the renal cases in spite of this show a low "d" reading. If in a case of this kind the reading should be 8, for instance, in view of the concentration of the urine we would be justified in assuming that were the quantity of the urine within normal limits, the reading would be lower. The effect of concentration on the "d" value may be noted in Case 7, Table 2. Here we have an approximately normal excretion of phenolsulphonephthalein and a high normal "d" reading, 32 on three occasions. It is probable that urine within normal limits in this case would have brought the reading to a lower "d" worth. In general, it may be assumed that only when a urine is abnormally large or abnormally small in quantity allowance need be made for dilution or concentration in judging the value of the actual "d" reading.

Rosenthal[14] has made an attempt to estimate what he terms the "absolute diastatic strength" of the urine. This he does by multiplying the twenty-four-hour total by the "d" reading and then dividing by 2; for example, daily output 1,500 c.c., 0.2 c.c. of urine digests 2 c.c. 0.1 per cent. starch solution, therefore the absolute diastatic strength =

$$\frac{1{,}500 \times 10}{2} = 7{,}500, \text{ or 500 per cent. concentration.}$$

I do not see that anything is gained by this method, and as Corbett aptly comments, "the results would vary out of all proportion to slight changes in the daily excretion," which in Rosenthal's series they do.

Another factor to be considered is the influence of fever on the "d" values, and here all observers agree that very high readings are found in acute infectious diseases. Rosenthal[14] demonstrates the influence of high temperatures in a case of nephritis which developed lobar-pneumonia. During the febrile period amylase was present in normal amounts; after subsidence of the fever no amylase could be found in the urine, while the clinical picture was at all times that of nephritis.

Having discussed the various conditions which may affect the action of amylase in the urine and having seen that in normal individuals in a twenty-four-hour specimen the "d" readings vary within narrow limits, it is appropriate at this point to summarize briefly actual figures obtained for the "d" values of normal twenty-four-hour urine specimens. Wohlgemuth,[7] in a large series of normal cases, says it varies between

$$d\frac{38^{\circ}}{30'} = 16 \text{ to } 32$$

never exceeding 64. Corbett,[8] working with slightly different dilutions, gives 6.6 to 33.3 with an average of from 10 to 24. Rosenthal,[14] whose method of calculating his readings is different, gives 10 to 25 when his results are translated into terms of the original Wohlgemuth method.

From repeated examination of eight normal cases and many other cases whose clinical condition gave no reason to suspect altered "d" readings, I have reached the conclusion that "d" = 8 to 32 is the normal range for twenty-four-hour urine. The large majority of the readings were between 16 and 32, as given by Wohlgemuth. I have never had a normal urine in which a reading of 64 has been reached.

Coming to the study of altered amylolytic power of the urine observations in the literature, so far it has been confined mainly to four conditions, that is, nephritis, diabetes, pancreatic disease and the so-called diabetes insipidus. Many other conditions have also been investigated, but the most positive and important results have been obtained in these four conditions.

NEPHRITIS

This includes all forms of the disease ranging from the acute type to the chronic (tubular, vascular or mixed) types, and includes also such conditions as pyelitis and renal calculus. Hirata,[33] working under Wohlgemuth's direction, produced sublimate, chromate and uranium nephritis in rabbits, estimating the amylolytic power of their urine before and after the production of nephritis. He found that the "d" values in all forms of nephritis were markedly decreased with a coincident rise on the "d" value of the blood, which was not always as marked as that shown in the urine. In view of the fact that these forms of experimental nephritis interfere mainly with tubular function, it would seem probable that amylase was excreted in largest quantities via this route.

This work on animals has been further substantiated by the investigations on patients suffering from various forms of nephritis. Wohlgemuth,[17] Wynhausen,[13] Marino,[15] Rosenthal,[14] and more recently Corbet[8] and Neuman[16] give distinctly low "d" readings for nephritis in general. Benczur[12] does not agree with the above-mentioned investigators, although he admits low readings in some of his cases of nephritis. He reports only eleven cases and five of these showed low "d" values. Two of the other cases showed very high readings. Benczur comes to the conclusion that no reliable information can be drawn from the test. It is interesting to note in this connection that although Benczur could not find any "essential" difference between $d\frac{37°}{24\text{ hr.}}$ readings of individual specimens and those of twenty-four-hour specimens, his five cases of nephritis with low readings were all twenty-four-hour specimens, while the other specimens examined, taken in hunger periods, when as Wohlgemuth shows, the "d" readings are highest, all give much higher amylase values.

Certainly the preponderance of evidence so far adduced demonstrates that in the large majority of so-called nephritides the amylase value of

33. Hirata, G.: Biochem. Ztschr., 1910, xxviii, 23.

twenty-four-hour specimens of urine is markedly below normal and in very few of the remaining cases does it exceed low normal limits. It must be admitted, on the other hand, that undoubted cases of severe chronic diffuse nephritis, proved by necropsy, and by the presence of every characteristic clinical symptom, have shown normal "d" readings, but these cases may also show one of the other functional tests to be normal.

In all of the thirty-five cases of renal disease shown in Table 1, the "d" value of the urine has been estimated one or more times. In all but two of the cases the phenolsulphonephthalein test of Rowntree and Geraghty has been made, and in the majority of instances on the day preceding the "d" estimation.

A word as to the technic of performing the phenolsulphonephthalein test in the First and Second Medical Divisions of the Presbyterian Hospital may be of service. The patient is given 200 to 300 c.c. of water twenty minutes previous to the administration of 6 mg. of the drug, which is given intramuscularly in all but a few instances, when it is given intravenously. The time of first appearance is noted. The specimen for this can usually be obtained by getting patient to void; if this is not possible, a catheter is used. Then the urines collected the first and second hours are estimated separately. The figures given are the totals of the first- and second-hour amounts. The time of appearance and the separate amounts for each hour are not deemed of sufficient importance in their relation to the "d" values to be tabulated. With the estimation of amylase, the quantity, specific gravity, reaction, albumin, casts and blood were noted in all twenty-four-hour specimens, not only on day of "d" estimation, but at intervals during their stay in the hospital. Albumin and casts are tabulated as an average finding in several examinations during the test periods or albumin as a separate finding when its relation to the "d" reading is important.

The diagnoses appended are clinical and made at the time of discharge of patient. Secondary conditions and necropsy findings are given when they occur.

From Table 1, if we consider eight as low normal limit, it will be seen that twenty-three of the thirty-five cases of nephritis, or 65.7 per cent., show persistent subnormal or absent "d" values. If we compare these values with the phenolsulphonephthalein readings we find that twenty of the corresponding cases also show a lowered phthalein excretion, assuming anything below fifty to be subnormal.[34] Of the remaining three cases, one (27) was a severe case of nephritis and the phenolsulphonephthalein test was not made, as it was not deemed advisable to

34. Cases 15 and 24 are here included as the later high readings for phenolsulphonephthalein were not explained clinically.

disturb the patient; while in the other two cases (14 and 32), which showed phenolsulphonephthaleins of 57 per cent. and 52 per cent., respectively, with "d" readings of four in each case, no definite theory can be advanced to explain the discrepancy, unless, as in Case 14, the mild degree of diabetes and secondary anemia can explain it. Low "d" readings in these conditions having been found by other observers, Marino,[15] Neuman,[16] Wynhausen,[13] etc. Case 32, however, cannot be explained on any such basis.

Of the twelve cases which do not show subnormal "d" values in every estimation, three show it in two or more readings and their average would be subnormal. Two of these three cases, namely, Cases 8 and 25, show low phenolsulphonephthaleins, whereas the other case (1) shows one lowered phthalein and two readings above normal. This latter case was one of severe nephritis and the patient died in a uremic condition.

This leaves nine cases of nephritis, as evidenced by clinical signs, in which there was a low normal or normal "d" reading. Of these, one (4) did not have the phenolsulphonephthalein test made. Of the remaining eight, five, that is, Cases 12, 16, 18, 22 and 26, gave normal "d" readings and slightly subnormal phthalein readings, while three cases, namely, 21, 23 and 35, gave normal "d" and phenolsulphonephthalein readings.

To summarize, then:

In thirty-three cases both tests were made.

In twenty-two cases subnormal readings were shown for both tests.

Three of the remaining eleven show diminished "d" with normal phenolsulphonephthalein (Cases 1, 14 and 32).

Five show diminished phenolsulphonephthalein with normal "d" readings.

Three of these cases (16, 18 and 26) show a diminution of phthalein, which was very little below normal, Case 18 having at one time 69 per cent. The remaining three agree in that they show normal "d" and phenolsulphonephthalein readings.

Case 17, J. T., calls for more detailed comment. I have included this case among those that give a low reading for both tests, because at the height of his kidney condition they both showed very low readings. This was in the latter part of January. At that time the edema was extreme, the urine quantities very small, blood-pressure was high and the patient was rapidly going into uremia. January 30 a double decapsulation of the kidneys was made, and from that time on until July, when he was discharged, his kidney condition improved remarkably. The edema disappeared, the urine increased and the blood-pressure fell. Both functional tests came from extremely low readings to high normal readings; one amylase reading, March 6, 1913, showed low normal limit, but immediately rose again. The patient developed pulmonary tuberculosis

a month after the operation, and although this improved slightly, it still persisted at the time of his leaving the hospital. Three high normal "d" readings were obtained before fever developed, which was persistent but slight.

In Cases 1, 8 and 25, we find that there is not absolute agreement in all of the "d" readings; taken as an average, they are below normal, and should be interpreted as such. In Case 1 it must be noted that the phthalein average was normal.

It is of interest further to note that in every case when the "d" value was normal with small amounts of albumin the phenolsulphonephthalein was also normal.

In Case 8, it is of interest to note that the reading of 16 was obtained during a period of marked clinical improvement, whereas the other readings were obtained during the reverse condition.

As regards the relationship existing between the "d" reading and the severity of the nephritis, I am unable to draw any definite conclusions. In this connection, Wynhausen[13] states that the lower the "d" reading the more severe the nephritis. Some patients with low and in some cases absent "d" readings, were discharged apparently improved. Of course, there has not been sufficient time in some cases to determine what the outcome will be, while in others there is no data as to what may have occurred after the patient left the hospital.

On the other hand, three patients with normal or high normal "d" readings have died. In one of these cases (No. 4) death was probably due to complicating disease. Excluding this case, it will be seen that nine of the eleven patients who died had low "d" readings.

CARDIAC DISEASE

In Table 2 nineteen cases of cardiac disease are tabulated. In some of these at certain times during which the patients stayed in the hospital, there were marked evidences of acute myocardial insufficiency. In all of the nineteen cases phenolsulphonephthalein and "d" readings were made, and in seven of the cases two phthalein readings were made, one at the time of acute decompensation and a second one later. Six of these cases showed low readings at the time of decompensation and normal readings later. This was rather a striking feature of these cases, a fact that has already been pointed out by Rowntree, Geraghty and Fitz,[35] who produced varying grades of chronic passive congestion of the kidneys in dogs, and found in the severe types of congestion a marked diminution in the phthalein output. This, Rowntree and Fitz[36] later confirmed in their clinical findings in a series of cardiac cases, which at the time of acute

35. Rowntree, Geraghty and Fitz: THE ARCHIVES. INT. MED., 1913, xi, 121.
36. Rowntree and Fitz: THE ARCHIVES INT. MED., 1913, xi, 258.

TABLE 2.—CHRONIC CARDIO-VALVULAR

Case	Name	Sex	Date	Amylase	Urine				
					Amt. c.c	Sp. Gr.	Albumin	Casts	Blood
1	M. F.	F.	10/31/13	16	1,020	1.015	0	0	.....
2	F. P.	M.	1/ 8/13	128	350+	1.025	H. Tr.	Hyal., gran.	Much
3	J. F.	M.	1/10/13	16	1,470	1.030	Trace	Hyal., gran.	Few R. B. C.
4	J. C.	M.	1/13/13	8	2,400	1.020	0	0	0
5	F. C.	M.	1/12/13	16	1,730	1.025	H. Tr.	Hyal., gran.	0
			1/15/13	32	1,290	.....			
6	J. H.	M.	1/16/13	16	1,530	1.015	F. Tr.	Hyal.	0
7	F. R.	M.	1/18/13	32	520	1.030	V. F.	0	0
			1/31/13	32	300	.....	Trace		
			2/ 6/13	32	450	.....			
8	S. C.	F.	1/22/13	32	605	1.029	V. H.	Hyal., gran.	R. B. C. few
			2/17/13	64	1.105	.....	Trace F. Tr.		
9	F. S.	F.	1/25/13	16	680	1.017	F. Tr.	0	0
10	R.	M.	2/ 5/13	2	1,150	.....	Trace	0	0*
11	J. V.	M.	2/ 4/13	8	3,210	1.030	H. Tr.	0	0
12	S. P.	F.	2/12/13	32	450	.....	V. F.	Hyal	0
			2/14/13	16	1,025	.....	Trace		
13	L. D.	F.	2/16/13	16	910	.....	V. F. Trace	0	0
14	D. C.	M.	2/17/13	32	1,745	.....	F. Tr.	Hyal.	0
15	P. D. L.	M.	2/18/13	16	880	.....	H. Tr.	Hyal., gran.	Many R. B. C.
			3/11/13	16	1,700	.....			
16	D.	F.	3/ 2/13	8	1,000	.....	V. F.	Few hyal.	0
			3/13/13	8	930	.....	Trace		
17	M. F.	F.	4/ 8/13	16	1,350	1.020	F. Tr.	Hyal., gran.	Occ. R. B. C.
			4/ 9/13	16	1,400	.....			
18	A. W.	F.	4/ 9/13	16	970	1.025	F. Tr.	0	0
19	K. W.	F.	1/15/13	16	440	1.015	H. Tr.	Coarsely gran., hyal.	Mod. R. B. C.

* Blood-pressure, systolic, 110.

Urine		Diagnosis	Result
Phenol-sulphone-phthalein Per Cent.	Date		
65	10/18/12	Chronic cardio-valvular disease. (This was during an acute attack of decompensation.)	Improved
8	11/ 5/12		
52	11/11/12		
65	12/ 6/12		
33	1/ 7/13	Chronic cardiac hypertrophy. Cardiac dilatation. Emphysema of lungs.	Died
43	1/ 8/13	Chronic cardio-valvular disease.	Died
53	1/11/13	Chronic cardio-valvular disease.	Improved
35	12/19/12	Chronic cardiac insufficiency and myocarditis.	Improved
62	12/23/12		
32	12/30/12	Chronic cardio-valvular disease; aortitis.	Improved
57	1/14/13		
47	1/16/13	Chronic cardio-valvular disease; mitral regurgitation; aortic regurgitation. (Necropsy diagnosis same as clinical.)	Died
4	1/20/13	Chronic cardiac insufficiency; hydrothorax.	Improved
43	2/15/13		
64	1/23/13	Chronic cardio-valvular disease; acute endocarditis (fever.)	Died
51	2/ 2/13	Chronic cardio-valvular disease; subacute articular rheumatism.	Improved
41	2/ 3/13	Chronic cardio-valvular disease; auricular fibrillation; aortic roughening and stenosis.	Improved
20	2/ 2/13	Obesity and fatty heart.	Improved
58	2/10/13		
84	2/14/13	Chronic cardio-valvular disease; cardiac hypertrophy and dilatation.	Improved
28	2/16/13	Chronic cardio-valvular disease; septicemia (fever); acute pericarditis.	Died
21	2/17/13	Chronic cardio-valvular disease; cardiac hypertrophy and dilatation.	Improved
65	3/ 7/13		
56	3/ 1/13	Chronic cardio-valvular disease.	Improved
53	3/12/13		
64	4/ 7/13	Chronic cardio-valvular disease.	Improved
48	4/ 7/13	Chronic cardio-valvular disease; hydrothorax.	Improved
34	1/17/13	Chronic cardio-valvular disease.	Died
Appearance after one hour.			

insufficiency showed low phthalein readings, with subsequent normal readings when the symptoms of decompensation cleared up and there was no concomitant nephritis.

In only one case in Table 2 have synchronous "d" and phenolsulphonephthalein readings been made during the time of decompensation, and later when compensation was restored. In this case (No. 8), when the phthalein was 4 per cent. the "d" value was 32, while nearly a month later the phthalein had increased to 43 per cent. and the "d" reading to 64. In another case (No. 19), during decompensation, when the phthalein was low, 34 per cent., the "d" reading was 16, or normal.

In view of the fact that at the time of acute decompensation with diminished phenolsulphonephthalein excretion there is nearly always a large amount of albumin and many red blood-cells, we would not expect to find low "d" readings, and in the few cases observed this has proved to be the case; in fact, it has been rather high normal. So that we must conclude that the "d" reading shows very little if anything as regards functional activity during the periods of decompensation. If it can be shown that during the period of passive congestion, the urine, in spite of the presence of albumin and blood, gives a reading of 8 or 16, and then later when these two constituents are diminished or absent and the heart condition has improved, the reading is still the same or perhaps increased to 32, we might readily assume that what in other circumstances would be taken for a normal reading had really been an expression of impaired function.

Generally speaking, twelve out of nineteen cases show normal phenolsulphonephthalein (after the period of decompensation, readings of 48 per cent. and 47 per cent. included) and also normal "d" readings. Of the remaining seven cases, three (3, 8 and 11) showed only slightly impaired phthaleins with normal "d" readings and in none of these cases were further phenolsulphonephthalein tests made.

Three cases showed phthaleins ranging from 28 to 34 and normal "d" readings. Of these last three cases, Case 2 showed very high "d," 128, but there was much blood in the specimen. Case 19 showed marked passive congestion of lungs and liver as well as kidneys during the stay in the hospital, and while the "d" reading is 16, the possible influence of concentration of the urine, blood and albumin must be noted. The third case in this group is one where the phenolsulphonephthalein was 28 per cent. and the "d" reading 16. Here there is a possible influence exerted by fever.

There is one atypical case in this group, and that is Case 10. Phthalein reads 51 per cent. and "d" 2. That there was any renal involvement in this case was certainly not demonstrable clinically, either at the time of admission to the hospital or at any subsequent time. It must remain unexplained.

In this series of cardiac cases there are only three in which the influence of urinary concentration should be considered, namely, Cases 7 and 19. In both these cases we may consider a lower reading than that given to be possible, but the question as to what the "d" readings might have been, had the urine quantities been larger, was not determinable in either case. In Case 11, with 3,210 c.c. of urine and a reading of 8, a higher reading, let us assume, to 16 would still have been in accord with what other cases of this series show.

In Table 3 thirteen cases of varied clinical conditions are tabulated. In this table each case or each group of cases must be considered separately.

DIABETES

First of all let us consider diabetes. Only two cases are to be found in this table, while the other two are found in Table 1. It must be acknowledged that both cases in Table 1 cannot be considered as pure cases of diabetes. There was doubt in the minds of those who studied Case 14, R. P. (Table 1), as to whether the nephritis or glycosuric condition was the primary one. Also in Case 2, L. K. (Table 1), the question not only of nephritis but of dyspituitarism entered into the consideration. The glycosuria in this case was small but persistent, and failed to yield at all to dietary measures. We find that both these cases showed subnormal "d" readings with normal amounts of urine. The phthalein in one case, that of L. K. (Case 2, Table 1), was a shade under the normal, while with R. P. (Case 14) it was normal. The clinical findings all pointed to an underlying chronic nephritis, and for this reason I have classed them as nephritics.

Case 6, J. C., and Case 12, Wm. McG. (Table 3), were quite different, as the patients undoubtedly suffered from a primary diabetes mellitus, with large sugar outputs, and in Case 6 multiple furunculosis with diacetic acid and acetone in the urine. The urine quantity was low in Case 6, but a portion was lost; in fact, twenty-four-hour specimens were very hard to obtain. The patient had a normal "d" reading with little albumin and little blood, as did also Wm. McG.

No conclusions from these four cases are justified.

Foster,[4] as early as 1867, investigated amylase in the urine of diabetics, and concludes that its value does not exceed normal limits. Leo[37] and Benderesky[38] found amylase increased in urine of diabetics. Lépine[5] found it decreased in the same disease. Enriquez and Binet[39] found the amylase values high in diabetes, decreasing as the sugar content of the urine decreased. Loeper and Ficai[40] found it decreased, while

37. Leo: Verhandl. d. VII. Kongr. f. inn. Med., 1888.
38. Benderesky: Virchows Arch. f. path. Anat., 1890, 121, 554.
39. Enriquez and Binet: Compt. rend. hebd. Soc. de biol. de Paris, 1908, lxv, 577.
40. Loeper and Ficai: Arch. de méd. expér. et d'anat. path., 1907, xix, 722.

TABLE 3.—

Case	Name	Sex	Date	Amylase	Urine				
					Amt. c.c	Sp. Gr.	Albumin	Casts	Blood
1	A. N.	F.	10/22/12	4	Incomplete	1.020 to 1.032	V. F. Trace	Few hyal.	0*
2	J. W.	M.	10/30/12	8	1,590	1.016	V. F. Trace	Hyal., gran.	0
3	C. F.	F.	12/ 4/12	64	800	.....	V. F. Trace	0	0
4	M. G.	F.	12/ 3/12	32	1,600	.....	0	0	Many pus cells Alkaline (reaction) alkaline
			12/ 6/12	32	1,450	.....			
5	C. W.	F.	12/ 4/12	32	840	1.020	0	0	0
6	J. C.	F.	12/13/12	16	360+	1.024	Trace	Gran., hyal.	Sugar. Few R. B. C.
7	T. M. 7years	M.	1/15/13	2	830+	1.010	0	0	0
8	T. T.	M.	1/21/13	32	2,500	1.010	F. Tr.	Hyal., gran., epith.	Bile
9	A. D.	F.	1/22/13	8	1,545	1.020	F. Tr.	Hyal., gran.	Few R. B. C.
10	D. M.	F.	1/25/13	32	1,300	1.015	V. F.	Occ. hyal.	0
			1/30/13	32	940	.. ..	Trace		
			2/25/13	8	4,000	.....			
11	E. B.	F.	2/28/13	8	550+	1.025	V. F. Trace	Hyal., gran.	Very few R. B. C.
12	Wm. Mc C.	M.	3/12/13	16	1,300	1.040	Trace	0	0
			3/18/13	16	1,300	.....			
13	G. K.	M.	5/30/13	32	465	1.030	V. F. Trace	Occ. gran.	0

* Blood-pressure, 130 systolic.

Urine		Diagnosis	Result
Phenol-sulphone-phthalein Per Cent.	Date		
41	10/25/12	Brain tumor. (No necropsy.)	Died two days after bilateral decompression
63	10/30/12		
24	10/26/12	Multiple myelomata (Bence-Jones bodies in urine). Fractured ribs.	Improved
None made	.....	Syph. arthritis knee.	Improved
None made	.....	Pyelitis. Cystitis of pregnancy.	Improved
None made	.....	Exophthalmic goiter; glycosuria.	Improved
None made	.....	Diabetes mellitus; multiple staphylococcic abscesses (fever).	Improved
None made	.....	Diabetes insipidus.	Improved
None made	.....	Hypertrophic cirrhosis of liver; cholangitis; ascites.	Improved
58	1/21/13	Complete abortion; albuminuria of pregnancy.	Improved
69	2/12/13	Exophthalmic goiter.	Improved
None made	.....	Asthma.	Improved
None made	.....	Diabetes mellitus; syphilis.	Improved
47	5/26/13	Chronic bronchitis.	Improved

Clark[41] found it absent. These were the most important contributions to the literature on this subject prior to 1908, when Wohlgemuth proposed the "starch iodin" method. All investigations prior to this had lacked reliable and uniform methods of estimating amylase, consequently these results are questionable.

Wohlgemuth[17] with four cases, Wynhausen[13] with forty, Rosenthal[14] with ten and Marino[15] with ten, find generally low readings in diabetes, some cases showing entire absence of amylase. Corbett[8] confirms this. Benczur[12] denies any variation from normal. None of the preceding writers seem to appreciate the possible effect of the tremendous diuresis which usually accompanies this disease, as a factor in lowering the "d" reading, or if they do, they merely add that there seems to be no relationship. Corbett[8] does, but in spite of this, insists on subnormal readings for the majority of cases under treatment. Wynhausen[13] says that the lower the "d" reading the more severe the disease and the higher the reading the milder the disease. Another very important complicating factor, which is so often found in diabetes, is nephritis, and this in itself would account for low "d" readings. Wynhausen[13] and Rosenthal[14] acknowledge its presence in the large majority of their very low "d" readings, but fail to appreciate its importance. Marino[15] also merely alludes to it. Even in those cases in which no urinary evidences of nephritis are present, we cannot exclude varying degrees of kidney damage as evidenced, for instance, by decreased permeability for sugar itself, increased blood-pressure, etc.

In view of the great importance of these two factors, namely, extreme diuresis and nephritis, on the values of the "d" readings apart from any other condition, it does not seem justifiable in the light of our present knowledge to attribute the low "d" readings or even the absence of amylase to diabetes *per se*, but rather to regard them as evidences of a complicating condition.

Case 2, L. K., and Case 14, R. P. (Table 1), with low "d" readings, are certainly suggestive of the above, particularly when contrasted with Case 6, J. C. and Case 12, Wm. McG. (Table 3), who, without evidence of renal disease, give normal "d" readings.

Diabetes Insipidus.—Case 7, T. M. (Table 3), a child aged 7, is the only case of the kind that I encountered. Strauss[42] reported two cases in which not only was there no amylase found, but also no pepsin. The absence of the latter had only been met twice before, once in a case of uremia and the other in a case of carcinoma of the stomach. Rosenthal[43] reports a case in which he also failed to find amylase in the urine, except

41. Clark: Glasgow Med. Jour., 1905, June, 632.
42. Straus, H.: Deutsch. med. Wchnschr., 1912, iv, 163.
43. Rosenthal, A.: Berl. klin. Wchnschr., 1912, xlix, 1265.

in an occasional examination, when it was greatly diminished. Benczur[12] reports one case in which it was present in normal amount. Braunschweig,[44] working in Straus' clinic, has also failed to find pepsin in the urine of such patients. The case (No. 7) reported in Table 3 shows the amylolytic ferment to be greatly diminished.

M. G. (Case 4, Table 3) was not included under the nephritics, as the condition was confined to the right kidney alone, and at the time of these examinations there was no definite evidence of kidney involvement under cystoscopic examination. This evidence was present one month later.

A. N. (Case 1, Table 3) shows a possibility of some renal involvement, but aside from a very faint trace of albumin and a few hyaline casts, there was no definite evidence from a clinical standpoint. It must be regarded as an unexplained case of low "d" reading. The patient died two days after bilateral decompression; no tumor was found; there was no necropsy.

T. T. (Case 8, Table 3) had bile in the urine, and is interesting from the standpoint of what Wohlgemuth[45] has shown, namely, that bile in small amounts accelerates amylolytic action, while in large amounts it inhibitis the action.

It is to be regretted that no cases of pancreatic disease have been studied in view of the tremendously high "d" readings so uniformly found in these cases.

CONCLUSIONS

1. The amount of amylase in the twenty-four-hour specimen of a normal individual estimated by the Wohlgemuth method varies within very narrow limits, and for a given case is almost a constant factor.

2. The "d" value of the urine, in the vast majority of cases of chronic or acute nephritis, is subnormal or totally absent. In the preceding series of thirty-five cases, 77.1 per cent. show this.

3. Only in extreme variations in concentration under 500 and over 2,500 c.c. can this factor be considered to have appreciable influence on the "d" reading, and under these circumstances due allowance should be made in the interpretation of values of "d" obtained.

4. The majority of normal readings obtained in cases of chronic nephritis were from urines containing considerable albumin, seven out of nine cases with normal readings. This simply confirms the work of other investigators and leads us to assume that the presence of albumin itself increases enzymic activity or in the process of its excretion causes more enzyme to be given to the urine. Allowance must always be made for this factor in estimating the "d" value in nephritic urine.

44. Braunschweig: Dissertation, Leipsic, 1910.
45. Wohlgemuth, J.: Biochem. Ztschr., 1909, xxi, 447.

5. As a test for renal function in nephritis the readings for "d" agree remarkably well with those of the phthalein test, if we adopt a definite normal limit for both tests, namely, 50 per cent. for the latter and "d" = 8 for the former. The adoption of 50 per cent. as low normal limit for the phthalein test is one which I think is pretty well accepted by most clinical observers.

6. The degrees of impairment as indicated by percentages in phthalein readings and graded dilutions in the "d" estimation, do not permit comparison. This could hardly be expected.

7. Cardiac cases with symptoms of decompensation do not show lowered "d" values for urine, while the phthalein test is usually subnormal. The normal "d" reading in these cases is probably due to albumin or blood or both.

8. Final conclusions as to the relative merits of these two tests, both as to the diagnosis and prognosis, must await the results obtained from a larger number of cases. Meanwhile I would urge that the "d" test be given an exhaustive trial with relation not only to the phenolsulphonephthalein test, but also to other tests of renal function.

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THE CLINICAL STUDY OF HYPERCHOLESTERINEMIA *

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That lipoidal substances play an important rôle in the animal body is now generally recognized. They occur in practically all the body-tissues and the amounts are increased in sclerotic blood-vessels,[1] in the white plaques of retinitis,[2] in xanthomata, in old infarcts, in caseous tuberculous material and in the cholesteatomatous tumors of the ear and cranial cavity. The activity of certain anesthetics varies with their lipoidal solubility and hemolytic processes may be accelerated or retarded by the presence of lipoids. Quite recently a number of relatively simple methods have been described for determining the amounts of lipoids, and especially of cholesterin, in small quantities of blood or blood-serum. As a result, data concerning the quantity of cholesterin in normal and pathological bloods are now rapidly accumulating. It is the purpose of the present paper to review these recent studies of cholesterinemia and to present a series of personal observations.

The methods used for determining the amount of cholesterin in the blood depend on a variety of principles. Since free cholesterin protects red corpuscles from hemolysis by saponin, it has been proposed to estimate the amount of free cholesterin in the blood-serum by determining the degree to which the serum will protect washed red cells from hemolysis by saponin.[3] In most other methods the cholesterin is first extracted from the blood or serum and the amounts extracted are then determined either by direct weighing, by weighing after precipitation with digitonin, or by colorimetric methods. The extraction is of great importance because cholesterin is present in the blood largely in combination with fatty acids or other substances and the amount extracted depends on the degree to which these combinations are broken up. For this reason the simple extraction of dried blood or blood-serum in the Soxhlet apparatus

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1. Windaus: Ueber den Gehalt normalen und atheromatösen Aorten an Cholesterin und Cholesterinester, Ztschr. f. physiol. Chem., 1910, lxvii, 174.

2. Chauffard, A., de Font-Réaulx and Laroche, G.: Nature cholestérinique des plaques blanches rétiniennes dans un cas de rétinite albuminurique, Compt. rend. Soc. de Biol., 1912, lxxiii, 283.

3. Boidin, L., and Flandin, C.: Procédé rapide de diagnostic de l'hypercholestérinémie à l'aide de la saponine, Compt. rend. Soc. de Biol., 1912, lxxii, 28.

uniformly fails to yield the total free and combined cholesterin present. The method which we have used is based on the methods described by Grigaut[4] and by Weston and Kent.[5] In extracting we followed the method of Grigaut, in which a preliminary treatment of the blood-serum with an alkaline alcoholic solution at a high temperature is used to break up the cholesterin compounds. The colorimetric estimation of the amounts of cholesterin subsequently extracted was made according to the modification of Salkowski's test described by Weston and Kent.

TECHNIC

In brief, our procedures were as follows:

Two c.c. of blood-serum were placed in a pressure bottle of 150 c.c. capacity. To this was added 20 c.c. of 1 per cent. solution of potassium hydroxid dissolved in 50 per cent. alcohol. The cover was screwed down and the whole placed in a boiling water-bath for from fifteen to twenty-minutes. After removal from the water-bath, the contents of the pressure bottle were allowed to cool and were then shaken with 50 c.c. of ether. The ether was decanted into a separating funnel and 30 c.c. more of ether was added to the remaining fluid and shaken vigorously as before. This was again decanted into the funnel and any aqueous liquid which separated from the ether was removed. This was then washed with 80 c.c. of distilled water. The ethereal extract, after separation from the wash water, was poured into an evaporating dish and evaporated nearly to dryness, leaving behind the small yellow oily droplets containing the cholesterin. Five c.c. of chloroform (Merck's blue label) was then placed on the evaporating dish and rotated carefully so as to dissolve the oily droplets as completely as possible. This chloroform solution was transferred to a convenient receptacle, and a second 5 c.c. of chloroform was then used to wash the evaporating dish and were added to the first 5 c.c.

The amount of cholesterin in the chloroform solution was determined by comparing its color reaction with those of cholesterin chloroform solutions of known strength. These standard solutions were prepared by dissolving Merck's cholesterin in pure chloroform (Merck's blue label) and by preparing a series of dilutions of varying strength so that the amount of cholesterin in 1 c.c. of chloroform varied from 0.0002 to 0.0004 gm. A set of test-tubes of uniform bore were arranged in a rack and 1 c.c. each of the known solutions of cholesterin were added in ascending series, as was also 1 c.c. of the cholesterin solution prepared from the blood-serum. It was often necessary to dilute the latter so that the amount would fall within the scale of the known quantities. To each tube was now added 0.1 c.c. of concentrated sulphuric acid, and the mixture was thoroughly shaken. After thirty minutes 1 c.c. of chloroform was added to each tube and after being placed for fifteen minutes in a dark room, the color of the unknown solution was compared with that of the known. This method was found to be exceedingly sensitive and differences in the original fluid of 0.00005 gm. per c.c. could be detected. Successive readings from the same serum also gave concordant results, and even after several days' standing, little or no diminution in the amount of the cholesterin in the serum could be discovered.

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4. Grigaut, A.: Sur le dosage de la cholestérine dans les tissus, Compt. rend. Soc. de Biol., 1911, lxxi, 441.

5. Weston, P., and Kent, G.: Determination of the Cholesterol Content of Human Serum by the Colorimeteric Method, Jour. Med. Research, 1912, xxvi, 531.

THE AMOUNT OF CHOLESTERIN IN NORMAL BLOOD

The amounts of cholesterin in normal blood-serum found by various observers who have used methods similar to the preceding, have been fairly concordant. Thus Grigaut placed the normal limit from about 1.2 to 1.8 gm. per liter of blood-serum, Weston and Kent[5] found from 1.17 to 2.97 with an average of 1.82 gm., Henes[6] found from 1.4 to 1.8 gm. per liter of blood-serum, and Widal, Weill and Laudat[7] found 1.74 and 1.95 in two normal fasting individuals. Iscovesco[8] has described a more elaborate extraction method, which apparently yields somewhat larger quantities than the above.[9] As will be seen from Table 1, the cholesterin in normal blood-serum as estimated by the method which we used, varied between 1.20 and 1.75 gm. per liter. Amounts of 2.0 gm. per liter or over may be regarded as definitely pathological. When those with marked thickening of the peripheral arteries and high blood-pressure were excluded from consideration, the age of the individual did not influence the amount of cholesterin in the serum. This is of interest in view of the fact that Wacker[10] observed an increase in the cholesterin content of the reserve fat of aged persons, and Robertson and Burnett[11] have advanced the view that an accumulation of cholesterin in the body may account for the well-known incidence of carcinoma with advancing age.

TABLE 1.—CHOLESTERIN IN NORMAL BLOOD-SERA

Age	Observations	Amount in Gm. per Liter
10-19	1	1.40
20-29	5	1.60-1.27-1.75-1.45-1.50
30-39	3	1.65-1.25-1.35
40-49	1	1.20
50-59	3	1.45-1.55-1.20
60-69	4	1.30-1.20-1.30-1.35

The cholesterin of the blood is not distributed evenly between the plasma or serum on the one hand and the red corpuscles on the other. Iscovesco[12] found varying relations between the two. Henes[6] found that on the average 54.5 per cent. of the blood cholesterin was present in the

6. Henes, E.: Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei inneren Erkrankungen, Deutsch. Arch. klin. Med., 1913, cxi, 122.

7. Widal, Weill and Laudat: La lipémie des brightiques, Semaine méd., 1912, xxxii, 529.

8. Iscovesco, H.: Compt. rend. Soc. de Biol., 1912, lxxii, 257.

9. Defaye: La cholestérémie, Etudes cliniques, Univ. de Bordeaux, No. 126, 1911-1912. Quoted by Henes.

10. Wacker, L.: Ztschr. f. physiol. Chem., 1912, lxxx, 383.

11. Robertson and Burnett: Preliminary Communication on the Part Played by Cholesterol in Determining the Incidence of Carcinoma, Proc. Soc. Exper. Biol. and Med., 1913, x, 140.

12. Iscovesco, H.: Les lipoides du san: Dosage comparatifs des lipoides des globules frais et de sérum, Compt. rend. Soc. de Biol., 1912, lxxii, 985.

serum and 45.5 per cent. was in the corpuscles, so that when the serum was used for determinations the results were higher than when the whole blood was used. Grigaut and L'Huillier[13] obtained similar results in normal individuals, but they found that in pathological conditions the amounts in red blood-corpuscles remained fairly constant, even when the amounts in the blood-serum varied widely. For this reason the blood-serum is, as a rule, a more sensitive indicator of pathological changes than is the whole blood, and we have, therefore, made all of our determinations with blood-serum.

A number of authors have studied the effect of cholesterin ingestion on the cholesterin content of the blood. While some have failed to observe any relation between diet and cholesterinemia or between the amount of cholesterin taken by mouth and the amount in the blood, a number of recent workers have confirmed the opinion of those who have held that the cholesterin of the body is derived, in part at least, from the cholesterin in the food.[14] Thus Grigaut and L'Huillier[15] were able to raise the cholesterin content of a dog's blood from 1.8 to 3.0 gm. per liter by feeding 1 gm. of cholesterin a day, and in another animal the content was raised from 1.8 to 3.8 by feeding 2 gm. of cholesterin a day. After the feeding was discontinued the amounts of cholesterin in the blood-serum returned to normal rather rapidly. Similar observations with similar results have been made on man by Widal, Weill and Laudat, by Henes and by Lemoine and Gérard.[16] The cholesterin content of the blood may be raised either by feeding pure cholesterin or by giving a diet rich in this substance.

PATHOLOGICAL VARIATIONS IN THE CHOLESTERIN CONTENT OF THE BLOOD

It has long been known that the serum of certain patients is milky instead of being clear. These lactescent serums are in general associated with increases in the amounts of lipoid substances in the blood as determined by chemical methods, and in general also with hypercholesterinemia. Widal, Weill and Laudat[7] have shown, however, that the lipoids may be increased even though the serum is not milky and that no close parallelism exists between the degree of lactescence and the amounts of lipoids determined chemically.

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13. Grigaut and L'Huillier: Taux comparé de la cholestérine des hématies et du sérum dans le sang normal et pathologique, Compt. rend. Soc. de Biol., 1912, lxxiii, 202.

14. Doree, Gardner, Fraser, Ellis: Origin and Destiny of Cholesterol in the Animal Organism; a series of papers in the Proc. Royal Soc., 1908 to 1912.

15. Grigaut and L'Huillier: Hypercholesterinémie d'origine alimentaire chez le chien, Compt. rend. Soc. de Biol., 1912, lxxiii, 304.

16. Lemoine, G., and Gérard: Variations du taux de la cholestérine par rapport a l'alimentation, Bull. et mém. Soc. méd. d. hôp., 1912, 931.

Hypercholesterinemia has been frequently encountered in diabetes. Grigaut and Chauffard mention such an increase frequently. Bürger and Beumer[17] found an increase in four out of five diabetics, three of whom had milky serums. Henes found an increase in two out of seven patients. Apert, Pechry and Rouillard[18] were unable to find any definite increase in most of the diabetics whom they examined.

Our own observations on patients with diabetes are shown in Table 2. It will be seen that pathological increases of the cholesterin were present in six of ten patients, and that the largest amount occurred in a patient with diabetic coma. In two of the patients the cholesterinemia was increased after the sugar had been removed from the urine by placing the patients on a standard Von Noorden carbohydrate-free diet. Whether this rise was due to an increased amount of cholesterin in the diet or to an increased mobilization of lipoids already in the body, I am unable to say.

TABLE 2.—CHOLESTERINEMIA IN DIABETES

Name	Age	Blood-pressure	Sugar in urine	Cholesterin in gm. per liter	Remarks
Str.	20	120	7.0%	3.2	Severe case.
Bri.	56	145	4.5%	4.15	Coma. Mastoiditis.
LaF.	39	130	+	2.8	Diabetic gangrene.
			0	3.3	
Wil.	63	175	+	2.25	Arteriosclerosis.
McB.	53	135	+	1.7	Mild case.
			0	1.9	
Wic.	38	130	6.8%	2.8	Severe case.
Fee.	8	110	++	3.	Severe case.
Dib.	58	135	+	1.3	Very mild case.
Bar.	40	140	+	1.75	Very mild case.
Hil.	30	?	+	1.8	Mild case.

In jaundice due to an obstruction of the common bile duct there is uniformly present a hypercholesterinemia. Chauffard, LaRoche and Grigaut[19] have ligated the common bile duct in the dog and have found that the amounts of cholesterin in the serum rose from the normal of 1.75 gm. to amounts which varied between 2.4 and 5.4 gm. per liter. These same authors[20] have shown that hypercholesterinemia may also result from a clinical obstruction of the common bile duct, whereas in hemolytic jaundice the amount of cholesterin in the blood-serum is not increased. In five patients with obstructive jaundice whom we have

17. Bürger, M., and Beumer: Zur Lipioidchemie des Blutes, Berl. klin. Wchnschr., 1913, xx, 112.

18. Apert. Péchery, and Rouillard: Mesure de la cholestérinémie chez les diabétiques, Compt. rend. Soc. de Biol., 1912, lxxii, 822.

19. Chauffard, Laroche and Grigaut: Recherches expérimentales sur la cholestérinémie après ligature du cholédoque, Compt. rend. Soc. de Biol., 1913, lxxiv, 1093.

20. Chauffard, Laroche and Crigaut: Le taux de la cholestériné mie chez les hépatiques, Compt. rend. Soc. de Biol., lxx, 1911, 20.

studied there were definite increases in the amount of cholesterin in the blood. It seems evident, therefore, that common duct obstruction will lead to an increased amount of cholesterin in the circulation. Whether this is dependent entirely on a resorption of the bile or whether it is due in part to an associated disease of the liver, does not seem to be established at the present time.

TABLE 3.—CHOLESTERINEMIA IN JAUNDICE

Name	Cholesterin in gm. per liter	Diagnosis
Wo.	3.50	Infectious (or catarrhal) jaundice.
Gr.	2.95	Common duct stone with jaundice.
Ch.	2.85	Common duct stone with jaundice.
Sh.	3.80	Malignant obstruction of the common duct.
Tri.	3.90	Malignant obstruction of the common duct.

Hypercholesterinemia occurs with frequency in patients with chronic Bright's disease, high blood-pressure and related conditions.[21, 7] I have devoted considerable attention to this group of cases with the hope that some relation might become evident between the hypercholestrinemia and the individual manifestations of cardiorenal disease. Our results which are shown in Table 4 have been arranged in the following order: the first four patients showed marked thickening of the peripheral arteries, but had no increase in blood-pressure and no albumin in the urine. The cholesterinemias in these patients were 2.25, 2.3, 1.80 and 1.95, respectively. The next group of patients showed chronic arterial hypertension without albumin in the urine. In this group the cholesterinemias were 2.0, 2.37, 1.95, 2.75, 1.85, 1.25, 3.2 and 3.3 gm. per liter. The third group includes those with chronic hypertension and albumin in the urine, but with good functional tests of the kidneys. In this group of patients, the figures were 2.0, 5.3, 3.85, 3.85, 1.25, 2.15, 1.75, 2.1, 2.25, 2.97. The final group includes those who showed more or less renal insufficiency as judged by the phenolsulphonephthalein test and an increase of hypobromite "urea" in the blood. They are arranged according to the degree of renal insufficiency, the more severe ones being placed last. The cholesterinemias in this group of patients were 3.5, 4.0, 1.35, 1.95, 1.85, 1.6, 1.73, 0.85, 0.8. In the first three of the preceding groups a hypercholesterinemia of moderate grade was encountered in the majority of the patients. Some of the lower figures may possibly have been due to an associated edema. It is interesting that we should have found an increase in the amount of cholesterin in two of four patients selected on account of a marked thickening of the peripheral arteries who

21. Chauffard, Laroche and Grigaut: Le taux de la cholestérinémie au cours des cardiopathies chroniques et des nephrites chroniques, Compt. rend. Soc. de Biol., lxx, 1911, 108.

TABLE 4.—Cholesterinemia in Vascular and Renal Disease

Name	Age	Blood-pressure	Urine	Peripheral Arteriosclerosis	Cholesterin in gm. per liter	Phthalein output	Hypobromite "Urea"
			GROUP I				
En.	59	145	neg.	marked	2.25	....	....
Her.	49	154	neg.	marked	2.30	71.2	.25
Rey	67	120	neg.	marked	1.95	....	....
Wal.	75	120	neg.	marked	1.80	....	....
			GROUP II				
Mus.	..	170	neg.	marked	2.00	75.0	.22
Mil.	68	180	neg.	marked	2.37	....	....
Dun.	53	180					
		210	neg.	marked	1.95	63.3	.31
Bri.	73	190	neg.	marked	2.75	....	....
McD.	77	240	neg.	marked	1.85	....	....
Lai.	56	210	neg.	marked	1.25	48.8	.59
					....	28.0	....
Rus.	59	210	neg.	?	3.2	60.5	.65
Fos.	49	180	neg.	neg.	3.33	35.9	.44
					....	59.	....
			GROUP III				
Cam.	38	210					
		130	Hy.	mod.	2.0	72.	.36
Hat.	43	230	casts				
		230	Alb. and casts	slight	5.3	40.	.48
Ske.	39	210	Alb. and casts	slight	3.85	....	.51
Rey.	46	212	Alb. and casts	marked	3.85	77.5	.31
Hep.	47	230	Alb. and casts	marked	1.25	60.0	.46
Dew.	65	205	Alb. and casts	marked	2.15	....	.5
Van.	58	170	Alb. and casts	marked	1.75	42.2	.38
Owe.	52	...	Alb. and casts	marked	2.10	74.7	.65
Ant.	45	235	Alb. and casts	Mod.	2.25	....	....
Mil.	44	265	Alb. and casts	.....	1.97	....	....
			GROUP IV				
Doa.	48	172	Alb. and casts	Neg.	3.5	26.2	.34
May.	26	250					
		230	Alb. and casts	Neg.	4.0	34.0	.71
Wald.	54	190	Alb. and casts	Mod.	1.35	23.9	.53
Mor.	47	204	Alb. and casts	marked	1.95	22.3	.80
Mur.	58	225	Alb. and casts	marked	1.85	12.	1.55
Jac.	48	170	Alb. and casts	Mod.	1.45	....	....
					1.6	....	....
					2.1	....	....
Jacks.	45	245	Alb. and casts	marked	1.73	6.8	2.02
Gar.	40	105	Alb. and casts	Mod.	.85	.0	4.39
Eclampsia..	..	...	Alb. and casts	.....	.08	....	....

showed no evident signs of kidney disease; for Chauffard[22] and Henes[6] found no definite relation between arteriosclerosis and cholesterinemia. In patients with high blood-pressure but without albumin in the urine and without other signs of nephritis, hypercholesterinemia is also common. Of the first three groups, the hypercholesterinemia is most marked in the third in which the high blood-pressure was associated

22. Chauffard, A.: Les dépots locaux de cholestérine et leur rapports avec cholestérinémie, Rev. de med., 1911, xxxi, 176.

with evident renal disease. The study of Group IV shows that when there is marked renal insufficiency, as measured by the phthalein test and by the accumulation of hypobromite "urea" in the blood, the cholesterin content of the serum tends to fall and may even become subnormal. Similar observations have been made by others,[21] and Widal, Weill and Laudat[7] stated that they were able to follow three patients in whom a fall of the cholesterin in the blood coincided with a rise of the incoagulable nitrogen. It seems evident from these observations that a hypercholesterinemia cannot be regarded as an index of renal insufficiency, for it may be present in cases without manifest renal disease, and it usually falls at the time of maximum retention of the urinary products. So far as our observations go, it would seem that a hypercholesterinemia may be associated with the degenerative processes in the blood-vessels without manifest renal disease.

Chauffard and his school have studied the amounts of cholesterin in the blood during acute and chronic infections, and they have found that whereas in febrile tuberculosis the amount of blood cholesterin is diminished,[23] in typhoid fever it tends to be increased during the later stage of the disease.[24] They have also shown that in the later stages of pregnancy there is an increased cholesterinemia.[25] I have made no special study of these conditions, but have determined the cholesterin content of the blood in various conditions selected at random. Of these I wish to mention especially the case of a young girl with multiple tumors in the subcutaneous tissues which clinically resembled neurofibromas who had 5.63 gm. of cholesterin per liter of blood-serum. Unfortunately, it was not possible to remove one of the tumors for microscopic examination.

THE RELATION OF CHOLESTERINEMIA TO LOCAL CHOLESTERIN DEPOSITS

It has been mentioned that in certain pathological conditions there are abnormal deposits of cholesterin in the body, and the question arises as to the relation which may exist between such deposits and an increased cholesterin content of the blood. It is conceivable, for example, that the local deposits may depend entirely on local conditions which either favor a deposit of cholesterin from normal body fluids or which may possibly lead to a local production of cholesterin. The cholesterin deposits in infarcted areas and in tuberculous caseous material seem to be due to such local changes; and it has been shown[23] that in tuberculosis the cholesterin of the blood is normal or diminished. On the other

23. Chauffard, Richet and Grigaut: La cholestérinémie au cours de la tuberculose pulmonaire, Compt. rend. Soc. de Biol., 1911, lxx, 276.

24. Chauffard, Laroche and Grigaut: Évolution de la cholestérinémie chez les typhiques, Compt. rend. Soc. de Biol., 1911, lxx, 70.

25. Chauffard, Laroche and Grigaut: Evolution de la cholestérinémie au cours de l'état gravidique et puerpéral, Compt. rend. Soc. de Biol., 1911, lxx, 536.

hand, the cholesterin deposits may be regularly associated with such marked degrees of hypercholesterinemia as to favor the view that they result in large part from a surcharging of the blood with this substance. In such cases they may well be compared with the tophi of gout and one may speak of a cholesterin diathesis. Multiple tuberous xanthomas have been shown to be associated with marked local deposits of cholesterin,[26] and they are known to occur especially in association with general conditions, such as diabetes and jaundice, in which marked degrees of hypercholesterinemia are apt to be present. Furthermore, they have been shown to be associated with high degrees of cholesterinemia,[27, 28] so that they seem to depend on a surcharging of the blood with this substance. According to Chauffard and Laroche,[29] a similar relation exists for the more common xanthelasmas of the eyelids which are frequently encountered in chronic jaundice, and in two of four cases these authors demonstrated that xanthelasmas were associated with hypercholesterinemia. Greater interest attaches itself to the relation which exists between hypercholesterinemia and the cholesterin deposits in the blood-vessels, the retinae and the arcus senilis corneae which are so often associated with diseases of the kidneys and of the arteries. We know that hypercholesterinemia is frequent in such patients, and one is tempted to attribute these degenerations in part at least to the hypercholesterinemia present,[30] and especially so as Anitschkou[31] has shown that experimentally one may produce similar changes in the arteries by the administration of cholesterin. On the other hand, the cholesterinemia is by no means constant in these patients, and when present it is usually of moderate degree. Should one assume, therefore, that the cholesterin deposits were secondary to changes in the blood, one must postulate that there had been times of greater cholesterinemia during which the deposits occurred. The proof of such an assumption is not easily furnished and at present it seems more plausible to assume that these cholesterin deposits occurred secondary to degenerative changes in the tissues. Nevertheless the frequent occurrence of hypercholesterinemia in such patients and the experimental work of Anitschkou has opened up the whole subject of the relation of arteriosclerosis to hypercholesterinemia and a solution of

26. Pollitzer, S., and Wile, U. J.: Xanthoma tuberosum multiplex, Jour. Cut. Dis., May, 1912.

27. Thibierge and Wiessenbach: Xanthome tubéreux disséminé et généralisé avec hypercholestéinémie, Bull. et mem. Soc. méd. d. hôp., 1911, xxxi, 93.

28. Legendre, Joltrain and Levy-Franckel: Xanthome disséminé et généralisé avec chéloides secondaires, Bull. et mem. Soc. méd. d. hôp., 1912, xxxiv, 539.

29. Chauffard and Laroche: Pathogénie du xanthélasma, Semaine méd., 1910, xxx, 241.

30. Lemoine, G.: Théorie de l'artério-sclérose basée sur la cholestérinémie, Bull. et mém. Soc. méd. d. hôp., 1912, xxxiii, 227.

31. Anitschkou: Die pathologischen Veränderungen innerer Organe bei experimentellen Cholesterinesterverfettung, Deutsch. med. Wchnschr., 1913, xxxix, 751.

this question is all the more urgent for the reason that should there be any relation between hypercholesterinemia and arteriosclerosis it would lead to an endeavor to control the cholesterin content of the blood as a prophylactic measure in the prevention of arterial degeneration.

CONCLUSIONS

By the method which we have used, the cholesterin in the blood of normal individuals is found to vary within rather narrow limits. It was definitely increased in obstructive jaundice, in six of ten patients with diabetes, and most patients with marked thickening of the peripheral arteries, chronic arterial hypertension and chronic nephritis. When, however, there is a marked functional insufficiency of the kidney, the cholesterinemia may fall to normal or even below normal. In a patient with multiple subcutaneous tumors (neurofibromas?) there was a marked hypercholesterinemia. Excepting in the case of obstructive jaundice, where the cause of the hypercholesterinemia is in part at least due to a resorption of bile, little is known about the etiology of pathological increases in the amount of cholesterin in the blood.

THE UREA CONTENT OF THE SPINAL FLUID WITH SPECIAL REFERENCE TO ITS DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE

A SERIES OF NINETY-SEVEN CASES *

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In a study of the literature concerning the urea content of the spinal fluid, we have been struck by the amount of work done on this subject by French clinicians as contrasted with its apparent neglect by German, English and American clinicians.

The normal quantity of urea in the spinal fluid, as indicated from a review of a considerable mass of material in the literature, varies between 0.01 per cent. and 0.05 per cent. Mollard and Froment,[1] in 1909, reviewed the literature up to that time and cited the works which follow in brief. Richet, in 1897, gave twenty-five analyses and stated "possibly urea." Deniges and Sabrazès, and Sabrazès and Binaud,[2] in 1895, reported two cases of tuberculous meningitis showing 0.015 per cent. and 0.035 per cent. of urea in the spinal fluid. Comba,[3] in 1899, reported two cases of acute uremia, in which there was an increase in the total nitrogen of the spinal fluid. Dirksen,[4] in 1900, reported four cases, one of uremia in which the urea content was 0.04 per cent., while three cases in which there was no uremia showed 0.01 to 0.015 per cent. Carrière,[5] in 1905, stated that he had found the normal amount of urea to be 0.01 to 0.015 per cent. Emery[6] gave the normal as 0.035 to 0.04 per cent., Widal and Froin[7] as varying between 0.015 and 0.035 per cent., Castaigne and Weil[8] from 0 to 0.15 per cent., Graham Forbes[9] as 0.035 to 0.04 per

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1. Mollard and Froment: Urée dans le liquide cephalorachidien et urémie Nerveuse, Jour. de Physiol. et de Path. Gen., 1909, ii, 263.

2. Sabrazès and Binaud: Traité de pathologie Générale de Bouchard 1897, vi, 650.

3. Comba: Clin. Med. Ital., 1899, No. 9, p. 555.

4. Dirksen: Etude sur la composition chemique et la concentration moleculaire du liquide céphalorachidien, Thèse de Paris, 1900 to 1901.

5. Carrière: Etudes sur le liquide céphalorachidien dans l'urémie nerveuse, Séances et memores de la Soc. de. Biol., 1905, p. 239.

6. Emery: Clinical Bacteriology and Hematology, Blakiston Sons & Co., 1912.

7. Widal et Froin: L'urée dans le liquide céphalorachidien de Brightiques, Gaz. d hôp., Oct. 25, 1904, p. 1182.

8. Castaigne and Weill: Considerations pratiques d'order clinique et therapeutique sur le liquide céphalorachidien des urémiques., Jour. méd. franç., 1911, v, 34.

9. Forbes: Pathology of the Cerebrospinal Fluid, Lavori e reviste di chimicae microscopia clinica, October, 1908, p. 33.

cent. Finally, Mollard and Froment asserted that normally the quantity of urea in the spinal fluid was negligible, but in Bright's disease it might increase to a point of diagnostic or prognostic significance. From the study of twenty-three cases collected at that time they concluded (a) that a notable increase of urea in the spinal fluid could not be considered as pathognomonic of uremia with involvement of the nervous system, since it might be found whenever the kidneys functionated improperly; (b) that a urea content attaining or exceeding 0.4 per cent. meant a pure uremia and foretold a rapidly approaching fatal outcome; (c) that a urea content below 0.4 per cent. did not permit of definite conclusions, but should be considered in conjunction with concomitant symptoms.

In 1910, Froment[10] reviewed the literature, included the report of cases in his preceding article with Mollard, and collected reports of thirty-four new cases, making in all fifty-seven cases reported up to 1910.

From the study of these cases, Froment drew the following conclusions:

That all pathological conditions without kidney involvement showed a negligible quantity of urea in the spinal fluid, namely, 0 to 0.015 per cent. and that it never attained 0.1 per cent., while in nervous uremia the content varied between 0.15 and 0.45 per cent.; that some cases without a definite picture of uremia showed a definite increase of urea, as for instance 0.25 per cent. to 0.29 per cent. in cases of arteriosclerosis or Bright's disease in which at necropsy there were found multiple cerebral softenings, cerebral hemorrhages or meningitis; that one could determine the association of retained urea and uremia even though other pathological states existed; that with a spinal-fluid urea attaining or exceeding 0.4 per cent. one could definitely say that a pure, or more rarely, an associated uremia existed and foretell a nearing fatal outcome. With less than 0.1 per cent. of urea the diagnosis of uremia should be rejected. If the urea content of the spinal fluid lay between 0.1 per cent. and 0.3 per cent. the condition was frequently but not always to be interpreted as a pure uremia while one could not reject all other diagnoses. Should there be uremia the prognosis was often favorable.

Since our series of ninety-seven cases is practically limited to spinal fluids, we have so far said nothing as to the urea content of blood. While the urea content of spinal fluid was being studied and reported that of the blood and body fluids was being concurrently investigated. In almost all cases the urea content of all these fluids was found to agree. There were occasional discrepancies, but these were largely to be explained by variations in the time of obtaining the fluid and in the methods of examination. All observers tend to the conclusion that the quantity of urea is practically the same in all body fluids under similar circumstances. In 1906, Javal and Adler[11] reported four cases with determinations of

10. Froment: Diagnostic et prognostic de l'urémie nerveuse par le dosage de l'uree dans le liquide céphalorachidien, Lyon méd., 1910, i, cxiv, 269.

11. Javal and Adler: La diffusion de l'urée dans les transudats de l'organisme. Application au diagnostic et au prognostic de l'urémie, Séances et Mém. de la Soc. de biol., 1906, lxi, 235.

the urea content of more than one body fluid, all tending to establish an accord. In 1910, Javal and Boyet[12] reported the examination of the body fluids in ten cases with practically an agreement throughout. Several authors reported isolated cases in which the urea content of blood and spinal fluid was about the same. It remained for Javal[13] to establish this fact. This he did as the following study will show. In all cases the different fluids were obtained at the same time and the urea content considered as that part of the total nitrogen decomposable by sodium hypobromite.

The estimation of urea was made on blood and spinal fluid in eighteen cases, on blood and edema fluid in four cases, on pleural fluid and edema fluid in two cases, on ascitic fluid and edema fluid in one case, on blood and pleural fluid in five cases, on pleural fluid and spinal fluid in three cases. In all of these the urea content was practically identical, the variation being negligible, usually about 0.005 per cent., occasionally 0.01 per cent. Javal himself regarded the uniformity as established.

Accepting this fact, Castaigne and Weill[8] state that inferences may be drawn from examination of the spinal fluid which will be identical with those drawn from examination of the urea content of blood. They also report four cases in which uremia terminated fatally and in which the spinal fluid urea varied from 0.115 per cent. to 0.767 per cent.; and twelve cases in which uremia terminated in recovery, temporary at least, in which the spinal fluid urea was 0.1 per cent. to 0.2 per cent. Finally, they state that the urea content never reaches 0.1 per cent. in normal states while in established uremia it may vary from 0.1 per cent. to 0.5 per cent., or even higher.

From the work of Widal[14] and further work of Javal[15] on the parallelism in the urea content of different body fluids, the variations in the urea of the spinal fluid assume an importance equal to that of the blood urea. Widal states that, with a blood urea content of more than 0.05 per cent., there is some retention, and that one can follow at times the gradual increase from 0.06 per cent. to 0.07 per cent., and so on upward. He regards a quantity of urea below 0.2 per cent. as justifying a prognosis for life of more than one year; a quantity between 0.2 per cent. and 0.3

12. Javal and Boyet: La Retention de l'uree et sa diffusion dans les liquides de l'organisme, Séances et Mém. de la Soc. de Biol., 1910, lxviii, 527.

13. Javal: Contribution Numérique à l'étude de la composition clinique de sérosités physiologiques et pathologiques de l'organisme chez l'homme, Jour. de phys. et de path. gén., 1911, p. 508.

14. Widal: Le prognostic dans le mal le Bright par le dosage de l'urée du sang. Les rémissions temporaires et trompeuses de l'azotèmie, Bull. et Mem. de la Soc. de Hôp. de Paris, 1911, xxxii, 627.

15. Javal: Le grande azotémie, ses formes, son evolution son prognostique etudies par le dosage méthodique de l'urée dans le sang et dans les serosités de l'organisme, Bull. et Mém. de la Soc. de Hôp. de Paris, 1911, xxxii, 485.

per cent. as indicating a survival of only weeks or months, and a quantity above 0.3 per cent. as indicating a not far distant fatal outcome. He cites eighteen cases in which the blood content of urea was 0.2 per cent. to 0.3 per cent. of urea. The longest survival was seven months, while thirteen patients died within two months. Of thirteen cases with a quantity above 0.3 per cent., all died within one month.

Javal, too, agrees with Widal that with a blood urea content above 0.2 per cent. the fatal outcome is a question of weeks or months. Of his twenty-one cases, the one that survived longest lived but twenty-one months. In agreement with Widal he cites cases with marked remissions, but always with an eventual fatal outcome.

In the year 1912, several authors reported the urea content of the spinal fluid in infants and children. Nobécourt and Darré[16] reported twelve cases, in all of which there was evidence of nephritis. Of five cases in which there was either simple albuminous nephritis or the type associated with retained chlorids, the urea of the spinal fluid was well within normal limits. In four cases conforming to the type of combined urea and chlorid retention, the minimum urea content of the spinal fluid was 0.044 per cent., and the maximum 0.083 per cent. In a third class, comprising three cases, the lowest figure on admission to the hospital was 0.123 per cent., and the highest 0.204 per cent. These three patients left the hospital greatly improved with the spinal fluid urea within the normal limits. The subsequent course of the disease in these patients was not known.

Nobécourt, Bidot and Maillet[17] report twelve examinations of the spinal fluid in infants. They concluded from these that a urea content above 0.1 per cent. is, as a rule, soon followed by death. Six infants in their series had over 0.1 per cent. and less than 0.2 per cent. of urea in the spinal fluid. The longest duration of life among the six infants was twenty-nine days. The urea content of the spinal fluid in three of the series was above 0.2 per cent., and the longest duration of life among these patients was three days.

Nobécourt, Sevestre and Bidot[18] reported fourteen new examinations of the spinal fluid in infants under one year of age. Five of these showed urea content of 0.04 per cent. to 0.06 per cent., all without apparent kidney lesions, with the exception of one (0.057 per cent. urea), which showed at necropsy lesions of the kidney epithelium and a little thicken-

16. Nobécourt and Darré: L'urée du liquide céphalorachidien dans les nephrites de l'enfance, Bull. et mém. Soc. de hôp. de Paris, January, 1912, p. 16.

17. Nobécourt Bidot and Maillet: Valeur prognostique de l'élévation du taux de l'urée dans le liquide céphalorachidienne des nourrissons, Bull. et Mém. de la Soc. de Hôp. de Paris, July, 1912, p. 47.

18. Nobécourt Sevestre and Bidot: L'urée dans le liquide céphalorachidien des nourrissons, Arch. de méd. des Enf., November, 1912, p. 826.

TABLE 1.—Pathological Conditions, Nephritis Clinically Excluded

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	33	0.02	Cerebral tumor. Death.	.....	Differential: Polymorphs, 15%; lymphocytes, 85%.
2	11/12	0.05	Tuberculous meningitis.	.....	Fluid bloody. One examination. No tubercle bacilli found.
3	3	0.027	Acute anterior poliomyelitis.	Paralysis of face, weakness of legs. Improvement.	Cells per c.mm., 5 Butyric acid test neg. Polys., 2%; lymphos., 98%.
4	37	0.053	Acute general tuberculosis.	.....	25 c.c. bloody fluid.
5	3	0.044	Tuberculous meningitis.	.....	12 c.c. clear fluid. Polymorphs, 3%; lymphos., 71%; endoth., 26%; NaCl, 0.642%.
6	3	0.083	Tuberculous meningitis.	.....	Lymphocytes, 100%. 10 c.c. clear fluid. Tubercle bacilli present.
7	3	0.029	Tuberculous meningitis.	.....	Tubercle bacilli present.
8	11	0.04	Pneumococcus meningitis.	.....	Pneumococci present.
9	18	0.033	Tuberculous meningitis.	.....	Tubercle bacilli present.
10	29	0.08	Syphilitic meningitis.	Wassermann positive in both blood and spinal fluid.	Differential: Lymphos., 94%. Butyric acid test positive.
11	8/12	0.043	Lobar pneumonia with convulsions.	.....	Butyric acid test negative. NaCl, 0.747%. Cultures sterile.
12	7/12	0.058	Pneumococcus meningitis.	Necropsy. No kidney involvement.	Pneumococcus present. NaCl, 66%.
13	13	0.053	Tuberculous meningitis.		
14	22	0.053	Suppurative meningitis. Mastoiditis.		
15	5½	0.04	Streptococcus meningitis. Mastoiditis.	.....	Streptococcus present.
16	2½	0.033	Tuberculous meningitis.	.....	Tubercle bacilli present.
17	11/12	0.022	Bronchopneumonia. Furunculosis.		
18	31	0.067	Meningococcus. Septicemia, infective endocarditis. Necropsy.		
19	41	0.033	Tuberculous meningitis.	.....	Tubercle bacilli present.
20	22	0.049	Otitis media, acute.		
21	6	0.036	Suppurative meningitis.		
22	6/12	0.035	Tuberculous meningitis.	.....	Tubercle bacilli present.
23	5	0.022	Catarrhal gastritis.	Convulsions, cause not determined.	
24	4	0.029	Acute general tuberculosis.	.....	No cells.
25	35	0.071	Disseminated myelitis.	Slight albuminuria. Bloood-pressure 110.	
26	5	0.026	Tuberculous meningitis.	.....	
27	22	0.049	Suppurative otitis media.	Albumin, faint trace, no casts.	

TABLE 1.—Pathological Conditions, Nephritis Clinically Excluded.—(Continued)

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
28	15	0.053	Bronchopneumonia.	Albumin, faint trace, no casts.	Normal.
29	2½	0.053	Tuberculous meningitis.	Drowsiness to coma.	
30	19	0.053	Tuberculous meningitis.	Albumin, faint trace, no casts.	Tubercle bacilli present.
31	6	0.019	Tuberculous meningitis.	Stupor.	Lymphocytes, 99%. No tubercle bacilli found.
32	15	0.024	Tuberculous meningitis.	No albuminuria. No casts.	Lymphocytes, 91%.
33	34	0.053	Erysipelas.	Hysteria.	Lymphocytes, 91%.
34	53	0.025	Chronic alcoholism. Cerebral edema.	Delirium tremens. No albuminuria. No casts.	
35	46	0.053	Cerebral glioma.	Necropsy. Kidneys normal.	
36	38	0.026	Tertiary syphilis. Gumma of lenticular nucleus.	Necropsy. Kidneys normal.	
37	..	0.053	Tuberculous meningitis. Suppurative otitis media.	Faint trace albumin. No casts.	Tubercle bacilli present.
38	3¾	0.035	Tuberculous meningitis.	Albumin, faint trace, granular casts.	Lymphocytes, 67%.
39	11	0.014 0.038	Cerebral tumor.	Operation. Trace albumin. No casts.	
40	31	0.053	Lobar pneumonia. Alcoholic delirium. Tuberculous meningitis.	Trace albumin.	Tubercle bacilli present.
41	7	0.01	Tuberculous meningitis.	.....	Tubercle bacilli present.
42	36	0.053	Bulbar palsy. Tertiary syphilis.	No kidney symptoms.	
43	48	0.059	Suppurative meningitis. Suppurative otitis media.	No renal symptoms.	Pneumococci present.
44	16	0.010	Acute tonsillitis. Chr. valvular cardiac disease.	Trace albumin, few hyaline casts.	
45	1	0.038 0.04 0.045 0.07	Chronic basilar meningitis.	Necropsy. No renal lesion.	
46	38	0.135	Acute general tuberculosis. Tubercular meningitis.	Necropsy showed only a few miliary tubercles of kidney. Some congestion of glomeruli and slight degeneration of tubular epithelium.	Tubercle bacilli present.
47	8	0.179	Tuberculous meningitis.	Duration two weeks. Delirium. Coma. Fundi show some congestion of discs. No albuminuria. No casts.	Tubercle bacilli present. Lymphocytes, 76%.
48	53	0.03	Locomotor ataxia.	.....	Wassermann positive.
49	26	0.018	Chronic pulmonary tuberculosis.		

TABLE 1.—Pathological Conditions, Nephritis Clinically Excluded.—(Continued)

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
50	40	0.115	Paresis.	Very slight albuminuria. Casts in one of three examinations. Blood-pressure 140. Eye-grounds normal. No nephritic history, no signs.	Wassermann positive.
51	2½	0.053	Enterocolitis.		
52	12	0.035	Chronic pulmonary tuberculosis.	Urine normal.	
53	8/12	0.041	Acute general tuberculosis.	Urine normal.	
54	3½	0.026	Acute general miliary tuberculosis.	.....	Tubercle bacilli present.
55	18	0.029	Fracture base of skull. Suppurative meningitis.		
56	21	0.107	Perithelioma of spinal cord.	No abnormalities of urine. No evidence of nephritis. Diagnosis by operation.	

ing of the connective tissue. One case showed 0.17 per cent. and 0.23 per cent. of urea in the spinal fluid on successive examinations. At necropsy there was some thickening of the connective tissue of the capsule and its capiliaries. The liver, on the other hand, showed marked fatty infiltration and some degeneration. There was one case which exhibited signs of meningitis that were followed by gastro-intestinal disturbances. The last case showed, in two examinations, 0.189 per cent. and 0.377 per cent. of urea in the spinal fluid. Death occurred three days after the second lumbar puncture. No necropsy was made.

With all these facts in mind our own series of ninety-seven examinations has been to us most interesting.

Our method of estimating urea has been as follows: To 120 c.c. of a mixture of 40 parts of ether and 80 of alcohol, all the spinal fluid available was added and allowed to stand twenty-four hours in a glass-stoppered bottle. The mixture was then filtered through smooth filter-papers, the latter being moistened with absolute alcohol. The bottle was then carefully washed and the precipitate cleansed at least four times with hot absolute alcohol. The filtrate was evaporated to a syrupy consistency. The residue was then taken up once more with absolute alcohol, filtered and reevaported to a very little syrupy liquid. This was taken up in distilled water and put into a small vial in the hypobromite apparatus. One c.c. of nitrogen gas then equalled 0.002694 gm. of urea.

TABLE 2.—Uremia Resulting in Death

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	47	0.120	Nephritis, chronic. Acute uremia. Death.	Albuminuric retinitis. Blood-pressure 240-300 mm. of mercury. No necropsy.	15 c.c. clear fluid. No cells.
2	45	0.062 Blood 0.07	Chr. interstitial neph. Acute uremia. General arteriosclerosis.	Albuminuric retinitis. albuminuria, casts, coma. No necropsy.	No cells. Butyric acid test negative.
3	32	0.436 Blood 0.365	Chr. interstitial neph. Acute uremia. Death.	Albuminuric retinitis. Convulsions. Blood-pressure 198 mm. Albuminuria, casts.	NaCl 0.802.
4	35	0.402 Blood 0.363	Chr. interstitial neph. Acute uremia.	Albuminuric retinitis. Blood-presure 180-230. Nausea, vomiting. Albuminuria, casts.	
5	43	0.571 Blood 0.624	Chr. interstitial neph. Acute uremia.	Albuminuric retinitis. Blood-pressure 204 to 220 of mercury. Necropsy.	No cells.
6	25	0.107	Chr. interstitial neph. Acute uremia. General arteriosclerosis.	Albuminuria and casts. Blood-pressure 170-240 of mercury.	
7	65	0.14	Chr. interstitial neph. Acute uremia.	Albuminuria and casts. Blood-pressure 199 mm.	
8	35	0.161	Chr. neph. Cardiac decompensation.	Albuminuria. Casts. Died cardiac death. Blood-presure 148-160.	
9	50	0.619	Chr. interstitial neph. General arteriosclerosis. Albuminuric retinitis. Uremia.	Albuminuria very slight. Occasional casts.	
10	40	0.311 Blood 0.343	Chr. interstitial neph. Acute uremia. Cardiac decompensation.	Blood-pressure 180 mm. of mercury.	Polymorphs., 99%.
11	35	0.402 Blood 0.303	Chr. neph. Uremia.	Albuminuria, casts. Nausea, vomiting. albuminuric retinitis.	
12	42	0.26	Chr. interstitial neph. Uremia. Cardiac decompensation.	General edema. Stupor. Necropsy.	
13	26	0.673 Blood 0.28	Chronic diffuse neph. Uremia.	Prolonged kidney history. Semi-coma. Anuria.	Polymorphs., 92%.
14	32	0.026	Chronic diffuse neph. Uremia.	Kidney history of two years. Edema, dyspnea, oliguria, headache, coma. Marked albuminuria.	
15	63	0.35 Blood 0.32	Chronic diffuse neph.	Headache, vomiting. oliguria, albuminuria. Coma.	

TABLE 2.—Uremia Resulting in Death.—(Continued)

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
16	31	0.087	Chronic parenchymatous nephritis.	Stupor. Albuminuric retinitis. Marked albuminuria. Many casts. Blood-pressure 195-225 mm.	Polymorphs., 83%. NaCl 0.77%.
17	27	0.525 Blood 0.538	Chr. interstitial neph. Acute uremia. Cardiac hypertrophy.	Blood-pressure 158-192. Marked albuminuria. Casts, convulsions, coma.	
18	42	0.177	Chr. interstitial neph. Cardiac hypertrophy. Uremia.	Headache. Systolic blood-pressure 185-235 mm. Albuminuric retinitis. Stupor.	
19	32	0.298 Blood 0.308	Chr. interstitial neph. Empyema. Frontal sinus.	Marked albuminuria. Many casts. Systolic blood-pressure 138-195 mm.	
20	33	0.33 Blood 0.49	Chr. interstitial neph.	Albuminuric retinitis.	
21	25	0.453 Blood 0.471	Chr. interstitial neph.	Convulsions. Retinal hemorrhages. Blood-pressure 178-190 mm.	

All the determinations were made by one of us (S. G.), using always the above method. The disagreements in the amounts of blood and spinal fluid urea that are occasionally reported, are probably due to the fact that the determinations were not made at the same time.

The cases, as may be seen from the tables, are arranged in four groups: (1) cases in which nephritis could be clinically excluded; (2) cases in which death was caused by uremia; (3) cases in which clinical nephritis did not terminate fatally, and (4) pathological conditions with a diagnosis other than uremia, from which, however, nephritis could not be excluded.

Of cases belonging to Group 1; in which nephritis could be excluded, there were fifty-six. Thirty-three of these cases showed less than 0.05 per cent. urea in the spinal fluid; fifteen cases 0.05 to 0.06 per cent.; four cases showed 0.067 per cent., 0.071 per cent., 0.08 per cent. and 0.083 per cent., respectively, with no satisfactory explanation, and four cases show, respectively, 0.135, 0.179, 0.115 and 0.107 per cent. In none of the last four was there sufficient ground to explain the high urea content.

In the second group, which comprises twenty-one cases in which uremia was present, the constant high percentage of urea in the spinal fluid was very striking. In thirteen cases it was above 0.2 per cent., in

five cases between 0.1 per cent. and 0.2 per cent., and in three cases under 0.1 per cent. Two of the last three were, however, above normal.

In Group 3 there were eight non-fatal cases of nephritis. The two patients in this group (Nos. 1 and 2), who showed marked increase in the spinal fluid urea, left the hospital with little if any improvement. The history of these two cases in which there was high urea content was

TABLE 3.—NEPHRITIS NOT TERMINATING IN DEATH

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	49	0.22	Chronic uremia. Chr. interstitial nephritis. Gen'l arteriosclerosis.	Albuminuria, casts. Headache, vomiting. Unimproved.	25 c.c. clear, no cells. Butyric acid test negative.
2	37	0.193	Chr. interstitial neph. Albuminuric retinitis. Optic neuritis.	Headache, vomiting, unconsciousness, weakness. Slight albuminuria. Few hyaline casts. Blood. Improvement slight.	
3	55	0.035	Chr. interstitial neph. Acute uremia.	Moderate edema. Slight edema of retina. Albuminuria marked. Casts many. Blood-pressure 107-208. Greatly improved.	
4	24	0.025	Chr. interstitial neph.	History of very marked albuminuria two years previously. Headache for two years. Slight albuminuria. Occasional casts. Slight edema. Greatly improved. Eye-grounds normal.	
5	51	0.051	Chr. interstitial neph. Cardiac hypertrophy.	Blood-pressure 180-185. Marked albuminuria. Slight edema. No nervous symptoms. Greatly improved.	
6	35	0.025	Acute nephritis. Acute pharyngitis. Acute bronchitis. Uremia.	Edema of legs and chest, nausea, dyspnea, convulsions, fundi normal, many casts. Apparently cured.	
7	39	0.06 0.05	Chr. interstitial neph.	Headache, vomiting, neuroretinitis. Systolic blood-pressure 168-220. Moderate albuminuria, considerable number of casts. Temporarily improved.	
8	46	0.08	General diffuse neph. Arteriosclerosis. Staphylococcus aureus. Pyemia.	Death due to sepsis. Necropsy.	

TABLE 4.—Pathological Conditions with Diagnosis other than Uremia, from Which, However, Nephritis Cannot Be Excluded

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	55	0.431	Cerebral hemorrhage. Diabetes mellitus.	Glycosuria. Acidosis. Urine shows heavy trace of albumin. No casts. Specific gravity 1.037.	Blood-tinged fluid. Polymorphs., 92%; lymphos., 8%.
2	35	0.07	General paresis.	Slight albuminuria. Casts. Blood, Wassermann strongly positive.	Wassermann strongly positive.
3	21	0.018	Nephritis (?) Neuroretinitis, both eyes. Myxedema (?)	Slight albuminuria. Occasional casts. Blood-pressure 100-110.	
4	38	0.048	Nephritis (?) Uremia (?)	Slight albuminuria. Many hyaline casts. No definite history.	22 c.c. clear fluid. Wassermann negative. Butyric acid test negative.
5	39	0.067	Dementia.	Convulsions. Hallucinations. Blood-pressure 110-130. Slight albuminuria. Casts in two of six examinations made.	Polymorphs., 35%; lymphocytes, 58%; large monos., 5%; eosinophils, 2%.
6	36	0.053	Old hemiplegia. Broken cardiac compensation. Uremia (?)	Albuminuria marked. Many hyaline and granular casts. Admitted moribund. Irrational. Temp 98 F. Eye-grounds normal.	Polymorphs, 98%.
7	2	0.358	Tuberculous meningitis.	Unconscious. Vomiting of two weeks' duration. No examination of urine. Blood-pressure not taken. Survived one day in hospital.	No tubercle bacilli found.
8	36	0.421	Acute general tuberculosis. Tuberculous meningitis.	Chronic alcoholism. Eye-grounds show only a blurring of discs. Slight albuminuria. No casts. Blood-pressure 110-120. Edema none. Septic temperature. Irrational.	No tubercle bacilli found.
9	37	0.153	Atrophy of optic nerves.	Headache, vomiting. Unconsciousness, three attacks. Slight albuminuria. No casts. Blood-pressure not taken.	
10	8/12	0.614	Tuberculous meningitis.	Duration six days. Vomiting, convulsions, coma. No Kernig. Some stiffness of neck. Slight dyspnea. No Babinski reaction.	No tubercle bacilli in three examinations of spinal fluid. First lymphocytes, 74%; second lymphocytes, 42%.
11	65	0.121	Chr. interstitial neph. ? Cardiac decompensation. Senility.	Trace of albumin in two of ten examinations. Hyaline casts in four examinations. No nervous symptoms.	
12	49	0.095	Diabetes mellitus. Ulcerative colitis. Chronic diffuse neph. General arteriosclerosis. Cardiac hypertrophy.	Albuminuric retinitis. Blood-pressure 197-220. Marked albuminuria.	

not subsequently followed, but in the light of experience the patients may be presumed to have survived only a short time.

Of the twelve cases tabulated under Group 4, cases 1, 7, 8 and 10 present interesting problems. Unfortunately, necropsies could not be obtained in any of them, and it is therefore impossible to exclude nephritis as a complication or indeed the principal cause of death, but we feel that the burden of proof lies with the clinician as regards diagnosis.

CONCLUSIONS

Our conclusions as to the interpretation which may safely be made from increased amounts of urea in the spinal fluid must remain, both diagnostically and prognostically, almost the same as those of the authors quoted.

1. A spinal fluid urea content higher than 0.2 per cent. indicates a severe uremia and a rapidly fatal termination.

2. A content between 0.1 per cent. and 0.2 per cent. means a rapidly fatal termination in the majority of cases of nephritis.

3. A content between 0.05 per cent. and 0.1 per cent. does not permit of any definite conclusions either as regards diagnosis or prognosis. Such a content is, however, suggestive of severe urea retention and must be taken into consideration in the diagnosis of the condition.

4. As to diagnosis we believe that the determination of the presence or absence of urea retention in the body fluids will go far to clear up certain difficult problems where the question of uremia enters into consideration.

We desire to express our thanks to the attending physicians and members of the house staff who have made this material available.

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THE GONOCOCCUS COMPLEMENT-FIXATION TEST AND ANALYSIS OF RESULTS FROM ITS USE*

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In recognition of the recent admirable work by Schwartz and McNeil on the complement-fixation test in gonococcic infections, the fact must not be overlooked that Müller and Oppenheim, in 1906, were the first to apply this reaction to a gonorrheal affection and consequently are entitled to the distinction of being termed the originators. The present popularity of this test has been the outgrowth of the suggestion made by Schwartz and McNeil — namely, that of the employment of a polyvalent antigen. As a result of their labors, these workers contend, and seem to have proved conclusively, through animal experimentation: (1) "that the different strains of the gonococcus differ markedly one from another — so much so that the antibodies produced in the body by the toxin of one strain will in many instances not bind the complement in the presence of an antigen prepared from another strain. Therefore, if only one strain is used in the preparation of the antigen, a great many negative results would be obtained in positive cases; (2) an antigen prepared from many strains fixes the complement whenever one of its component strains does so, and consequently the necessity of testing a serum against a number of antigens separately is avoided. It is not to be denied that there probably are other strains of gonococci differing widely from any present in the polyvalent antigen, so that at times a negative result will be obtained in a positive case."

While we recognize the fact that a negative reaction may mean nothing, in fact, may be erroneously contradictory, the significance, on the other hand, of a positive reaction has been so great — more specific, in fact, than when the lipotropic antigen, commonly employed in the performance of the Wassermann reaction, is utilized — that we have applied the test for the past few months in a large series of diverse cases with the most gratifying results. Without entering on any discussion of the theories governing fixation or deviation of complement and hemolysis, it is our purpose, at this time, merely to outline our own technic, desig-

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nating certain points of superiority which it may possibly possess over that employed by Schwartz and McNeil, and to submit the analysis and results of cases in which serums were subjected to the gonococcus complement-fixation test.

DISCUSSION OF TECHNIC

The technic utilized and advocated by Schwartz and McNeil in the performance of the complement-fixation test for gonococcic infections embodies what may be termed the minimal quantity method. That is, the smallest quantities of the component substances entering into the reaction are employed that are compatible with practicability. Other than as a matter of economy and questionable conservation of time, this method possesses no recommendation. In fact, from a comparative study of the results in a series of cases in which Schwartz and McNeil's method is contrasted with the technic analogous to the Wassermann reaction as employed by us, it has appeared that the advantage has always rested with the latter or larger quantity method, in that the hemolytic readings seemed to be easier of interpretation.[1] Moreover, we have been impressed by the fact that the quantity of antigen employed in the former case, as will be seen presently, is too great — being indeed as much as, and more than, that utilized by us with five to ten times the gross quantity of material.

Schwartz's latest method and the technic which we practiced for a time in comparison with our own gonococcus complement-fixation test is as follows, so far as the quantities of the ingredients participating in the reaction are concerned: (1) patients' serum, 0.02 c.c.; (2) salt solution, sufficient to equalize the volume in each tube; (3) antigen (routinely 0.3 c.c. in one tube and 0.15 c.c. in another tube, of a commercial preparation diluted 1 to 10). These quantities are determined by preliminary standardization with a fresh known negative and a known positive serum; the positive showing the true antigenic dose, and the negative the highest quantity of antigen which will allow complete hemolysis; in the actual test this large quantity of antigen is placed in one tube and one-half the quantity in a second tube; (4) complement 0.1 c.c. of a dilution 1 to 10; (5) ambocceptor, 0.1 c.c. representing twice the lowest quantity that will completely hemolyse 0.1 c.c. of the cell suspension with 0.1 c.c. of complement in one hour; (6) sheep's red blood-cells (5 per cent. suspension), 0.1 c.c. Incubation is made for one-half hour at 37 C.

1. If it be necessary or desirable to practice economy in the performance of the test, we would suggest, in preference to the very small quantities employed by Schwartz and McNeil, which are more or less tedious to manipulate, just half of the component materials as employed in our technic. We have resorted to this modification on several occasions with results just as satisfactory as those obtained by the regular method.

in a water-bath or for one hour in dry heat, before and after the addition of the hemolytic system.

The technic on which we have learned to place the greatest reliance is essentially that utilized by us in the performance of the Wassermann reaction, merely substituting the gonococcus specific antigen for the syphilitic lipotropic antigen, employing always the carefully standardized single complement unit and the routine standardization of antigen and amboceptor. Briefly, the steps in the daily procedure are as follows:

AUTHORS' TECHNIC

As previously stated, a detailed description of the fundamental serological principles involved in the complement-fixation or deviation reaction, will be omitted from this discussion. We shall submit, therefore, merely a table representing the routine procedure in the performance of the gonococcus complement-fixation test (Table 1).

We believe that the features of importance in the proper execution of this test are: the required inactivations, the exact standardization of the hemolytic amboceptor and suspension of sheep's red blood-corpuscles, and paramountly, the complement and antigen each time the reaction is undertaken.

ANTIGENS

The preparation of the various ingredients entering into the reaction will receive no consideration at this time—with one exception, namely, the antigen. This, however, is of such importance with respect to the gonococcus complement-fixation test that it must receive some discussion, since on the integrity and specificity of this antigen depends the whole value of the test in gonorrheal infections. The necessity of a polyvalent antigen is indisputable, presumably owing to the diversity of the strains of the gonococcus. The only question of importance is, how may this antigen be prepared to the best advantage? Schwartz and McNeil in their latest communication say that the "various strains of gonococci are grown on salt-free veal-agar, neutral in reaction to phenolphthalein; 24-hour old cultures are washed off the agar-slants with distilled water and the resulting suspension is heated for two hours in a water-bath at 56 C. It is then centrifuged and passed through a Berkefeld filter. No salt is added to this antigen until it is desired to use it, when it is made up to 0.9 per cent. strength by adding one part of 9 per cent. saline solution to nine parts of antigen. Following Schwartz and McNeil's instructions to the letter, we have prepared monovalent, trivalent and hexavalent antigens[2] and have employed them comparatively in a large series of cases

2. In the near future we shall report the results of our studies of various gonococcal antigens, variously extracted; also the results comparatively of non-specific antigens prepared from certain Gram-negative and Gram-positive diplococci, as the *Micrococcus catarrhalis*, the meningococcus, the pneumococcus, the *Streptococcus pyogenes*, etc.

with the result that the hexavalent preparation gave the highest percentage of positive results and in every way appeared to be the most reliable of the three antigens. Even with the hexavalent antigen,[3] prepared as described above, we have been forced, in comparative studies, to the conclusion that it has not been so useful or reliable as when prepared in the following manner: Forty-eight-hour old cultures of the same six strains of gonococci, grown on blood-agar, were washed off in sterile distilled water; shaken for one hour; and autolyzed for twenty-four hours in a

TABLE 1—

	No. Test Tube	Antigen (Dilution 1:10) c.c.	NaCl Solution (0.85%) c.c.	Patient's Serum (Inactivated) c.c.	Known Positive Serum (Inactivated) c.c.	Known Negative Serum (Inactivated) c.c.	Complement (Dilution 1:10) c.c.		Hemolytic Amboceptor (Antisheep) (Titre = 1:2,000) (Dilution 1:1,000) c.c.	Red Blood Corpuscles (Sheep's 5% Washed Suspension) c.c.
Tests for complement standardization.....	1	0.2 ?	1.3	...	...	...	0.2	Incubation at 37 C. for one hour.	1.0	1.0
	2	0.2 ?	1.2	...	...	...	0.3		1.0	1.0
	3	0.2 ?	1.1	...	...	...	0.4		1.0	1.0
	4	0.2 ?	1.0	...	...	...	0.5		1.0	1.0
Tests for antigen standardization and controls	5	0.05	1.5	...	0.1	...	0.4 ?		1.0	1.0
	6	0.1	1.4	...	0.1	...	0.4 ?		1.0	1.0
	7	0.2	1.3	...	0.1	...	0.4 ?		1.0	1.0
	8	0.3	1.2	...	0.1	...	0.4 ?		1.0	1.0
	9	0.2	1.3	...	...	0.1	0.4 ?		1.0	1.0
	10	0.4	1.1	...	...	0.1	0.4 ?		1.0	1.0
	11	0.6	0.9	...	...	0.1	0.4 ?		1.0	1.0
Tests and controls for the suspected serum	12	0.2	1.3	0.1	...	...	0.4		1.0	1.0
	13	0.2	0.9	0.1	...	...	0.8			
	14	0.2	1.3	0.1	...	...	0.4		1.0	1.0
	15	...	1.5	0.1	...	...	0.4		1.0	1.0
									1.0	1.0

thermostat at the temperature of 37 C. and heated in a water-bath at 60 C. for one-half hour. Before use, this antigen is diluted one to ten by the addition of 0.85 per cent. salt solution. In spite of our efforts[2] thus far, we have been unable to produce an antigen showing results quite as clean-cut, although they have been just as constant, as that marketed by

3. We are indebted to Dr. A. P. Hitchens of H. K. Mulford Co. for the six strains of gonococci employed in this work. It should be noted in this connection that it is assumed that the cultures are true gonococci, since their staining and morphological characteristics are identical with that micro-organism, although they grow readily on blood-serum or even on plain agar-agar. The dispute has arisen as to whether a Gram-negative diplococcus, growing in this wise, should or should not be designated as the *Micrococcus catarrhalis*.

Parke, Davis & Co. The probable explanation is that their antigen is made up from twelve strains of the gonococcus, while ours contains but six.[3]

ANALYSIS OF CASES TESTED

The result of our work has been little more than a corroboration of the reports that have emanated from Schwartz and McNeil[4] and those who have confirmed their results. We believe, however, that, by utilizing the technic herein described, we have added to the accuracy of the test

TEST REACTIONS

	Results (Immediately or Morning After Refrigeration)	Objects of the Reactions.
Incubation at 37 C. for one and one-half hours.	Incomplete hemolysis.....	To determine quantity of complement to be used in test proper.
	Incomplete hemolysis.....	To determine quantity of complement to be used in test proper.
	Complete hemolysis.....	To determine quantity of complement to be used in test proper.
	Complete hemolysis.....	To determine quantity of complement to be used in test proper.
	Incomplete hemolysis.....	To determine quantity of antigen to be used in test proper.
	Partial hemolysis.....	To determine quantity of antigen to be used in test proper.
	No hemolysis.....	To determine quantity of antigen to be used in test proper.
	No hemolysis.....	To determine quantity of antigen to be used in test proper.
	Complete hemolysis.....	To prove that the antigenic dose is not in itself anticomplementary.
	Complete hemolysis.....	To prove that twice the antigenic dose is not in itself anticomplementary.
	Incomplete hemolysis.....	To prove that thrice the antigenic dose is not in itself completely anticomplementary.
	No hemolysis..... (Positive reaction hemolysis =1 unit)	To determine quantitatively the degree of complement fixation.
	No hemolysis..... (Positive reaction hemolysis =2 units)	To determine quantitatively the degree of complement fixation.
	Complete hemolysis..... (Complete negative reaction)	Shows that there was no immune body present in the patient's serum with the aid of the antigen to fix the complement.
	Complete hemolysis.....	Proves that the immune body itself will not fix complement.

as applied by them and have thereby improved the findings to the credit of the test and its value in clinical diagnosis. To the increased positive results we attribute the accurate standardization of antigen on each occasion and the employment of a standardized single complement unit. For the sake of convenience, our results with respect to the serums tested, numbering in all 204, have been tabulated (Table 2).

4. Schwartz and McNeil: "The Complement-Fixation Test in the Diagnosis of Gonococcic Infections," Am. Jour. Med. Sc., May, 1911; "The Complement-Fixation Test in the Differential Diagnosis of Acute and Chronic Gonococcic Arthritis," ibid., September, 1912; "Further Experiences with the Complement-Fixation Test in the Diagnosis of Gonococcus Infections of the Genito-Urinary Tract in the Male and Female," ibid., December, 1912.

TABLE 2.—RESULTS WITH RESPECT TO SERUMS TESTED

KNOWN NON-GONORRHEAL AFFECTIONS

No.	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens				
		Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
1	Typhoid fever	.....	.....	.....	Negative	Negative
2	Typhoid fever	.....	.....	.....	Negative	Negative
3	Typhoid fever	.....	.....	.....	Negative	Negative
4	Tuberculous otitis media and pulmonitis	.....	.....	.....	Negative	Negative
5	Tuberculous otitis media and pulmonitis	.....	.....	.....	.....	Negative
6	Pulmonary tuberculosis	.....	.....	.....	Negative	Negative
7	Diabetes mellitus	.....	.....	.....	Negative	Negative
8	Diabetes mellitus	.....	.....	.....	Negative	Negative
9	Diabetes mellitus	.....	.....	.....	Negative	Negative
10	Acute streptococcic endocarditis	.....	.....	.....	Negative	Negative
11	Chorea; secondary endocarditis	.....	.....	.....	Negative	Negative
12	Malaria	.....	.....	.....	Negative	Negative
13	Syphilis	.....	.....	.....	.....	Negative
14	Congenital syphilis	.....	.....	.....	.....	Negative
15	Syphilis	.....	.....	.....	.....	Negative
16	Luetic rhinitis	.....	.....	.....	.....	Negative
17	Syphilis	.....	.....	.....	.....	Negative
18	Syphilis	.....	.....	.....	Negative	Negative
19	Normal, no symptoms of gonorrhea	.....	.....	.....	.....	Negative
20	Normal, no symptoms of gonorrhea	.....	.....	.....	.....	Negative
21	Normal, no symptoms of gonorrhea	Negative	Negative	Negative	.....	Negative
22	Tuberculous osteitis and pulmonitis	.....	.....	.....	.....	Negative
23	Chronic hypertrophic arthritis	.....	.....	.....	Negative	Negative
24	Subacute arthritis (sacro-iliac and elbow)	.....	.....	.....	Negative	Negative
25	Arthritis (both ankles); six weeks	.....	.....	.....	.....	Negative
26	Tuberculous arthritis (knee)	.....	.....	.....	Negative	Negative
27	Chronic synovitis (midtarsal)	.....	.....	.....	.....	Negative
28	Optic atrophy	.....	.....	.....	.....	Negative
29	Neurasthenia	.....	.....	.....	.....	Negative
30	Neurasthenia	.....	.....	.....	.....	Negative
31	Chancroid	.....	.....	.....	.....	Negative
32	Vesical calculus; cystitis	.....	.....	.....	.....	Negative
33	Hemiplegia	.....	.....	.....	.....	Negative
34	Myelitis; incontinence of urine	Negative	.....	.....	.....	Negative
35	Case of rape; no signs of infection	Negative	.....	Negative	.....	Negative

36	Epididymitis, possibly tuberculous, but undoubtedly gonorrheal	.....	.....	.....	Medium +	Medium +
37	Urine cloudy and full of shreds	Medium +	.....	.....	.....	Strongly +
	PATIENTS CLINICALLY CURED					
38	Several attacks of gonorrhea; no signs at present	.....	.....	.....	.....	Weakly +
39	Convalescent after treatment for 2½ years for chronic urethritis and prostatitis	.....	.....	.....	.....	Negative
40	Syphilis; had three doses of neosalvarsan; convalescent from chronic urethritis	.....	.....	.....	.....	Negative
41	Convalescent from chronic prostatitis	.....	.....	.....	.....	Negative
42	Convalescent from chronic urethritis, three attacks; first 3 years ago	.....	.....	.....	.....	Negative
43	Convalescent from first attack of gonorrhea 8 weeks previously	.....	.....	.....	.....	Negative
44	Convalescent from attacks of gonorrhea 13 and 2 years previously	.....	.....	.....	Negative	Negative
45	Gonorrhea several years ago; no symptoms now	.....	.....	.....	Negative	Negative
46	Clinically convalescent from gonorrhea acquired 2 years ago	.....	.....	.....	.....	Negative
47	Convalescent from urethritis and prostatitis; received 8 c.c. of antigonococcic serum 15 months ago for gonorrheal pleurisy	.....	.....	.....	Negative	Negative
48	Polyarthritis; has gonorrheal history	.....	.....	.....	.....	Negative
49	Gonorrhea three times; asserts a cure; complains of impotence	Medium +	.....	.....	.....	Strongly +
50	Gonorrhea 3 years ago; epididymitis 9 months ago; prostatorrhea; wants to marry	.....	.....	.....	.....	Negative
51	Gonorrhea three or four times; now clinically cured	.....	.....	.....	.....	Negative
52	Gonorrheal history; apparently cured	Negative	Negative	Negative	.....	Negative
53	Gonorrhea 5 months ago; cured	.....	.....	.....	.....	Negative
54	Contracted gonorrhea 1½ years ago; convalescent from chronic prostatitis	.....	.....	.....	.....	Negative
	CASES ACCIDENTALLY DISCOVERED. CLINICALLY CURED					
55	Confessed to gonorrhea 2½ years ago; under antisyphilitic treatment	Weakly +	.....	.....	.....	Weakly +
56	Luetic rhinopharyngitis; no inquiry as to gonorrhea	.....	.....	.....	.....	Weakly +
	ACUTE ANTERIOR URETHRITIS					
57	Gonorrhea of 12 hours duration (first attack)	.....	.....	.....	.....	Negative
58	Gonorrhea of 10 days' duration (first attack)	.....	.....	.....	.....	Negative
59	Acute gonorrhea (first attack)	.....	.....	.....	.....	Negative
60	Gonorrhea of 11 days' duration (first attack)	.....	.....	.....	.....	Negative
61	Gonorrhea of 7 days' duration (first attack)	.....	.....	.....	.....	Negative
62	Gonorrhea of 4 weeks' duration (first attack)	.....	.....	.....	Negative	Negative

TABLE 2.—Results with Respect to Serums Tested.—(Continued)

No.	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens: Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
	ACUTE AND SUBACUTE ANTERO-POSTERIOR URETHRITIS					
63	Gonorrhea of 6 weeks' duration (first attack)	.....	.....	.....	.....	Medium +
64	Gonorrhea of 5 weeks' duration (first attack)	.....	.....	.....	.....	Negative
65	Gonorrhea of 4 weeks' duration (first attack 10 years ago)	.....	.....	.....	.....	Negative
66	Gonorrhea of 2 weeks' duration (first attack)	.....	.....	.....	.....	Negative
67	Gonorrhea of 10 days' duration (first attack 1 year ago	.....	.....	.....	.....	Negative
68	Gonorrhea of 7 weeks' duration (first attack)	.....	.....	.....	.....	Negative
69	Gonorrhea of 4 weeks' duration (first attack)	.....	.....	.....	Negative	Negative
70	Gonorrhea of 6 weeks' duration (first attack)	.....	.....	.....	Negative	Negative
71	Gonorrhea of 7 days' duration (three previous attacks)	.....	.....	.....	Negative	Negative
72	Gonorrhea of 10 days' duration (six previous attacks)	.....	.....	.....	Negative	Negative
73	Gonorrhea of 5 week's duration (first attack 2 years ago)	.....	.....	.....	.....	Negative
	CHRONIC URETHRITIS PLUS ACUTE EXACERBATION					
74	Gonorrhea 1 year previously; received 8 c.c. of antigonococcic serum; duration of present attack is 4 weeks	.....	.....	.....	.....	Weakly +
75	Gonorrhea 2 years previously; duration of present attack is 4 weeks	.....	.....	.....	.....	Medium +
76	Gonorrhea 1 year previously; duration of present attack is 3 weeks	.....	.....	.....	.....	Strongly +
77	Gonorrhea 1 year ago; acute exacerbation at present	.....	.....	.....	.....	Weakly +
78	Gonorrhea 8 times previously; duration of present attack is 17 days	Strongly +	Weakly +	Strongly +	.....	Strongly +
79	Gonorrhea 5 years ago; duration of present attack 10 days	.....	.....	.....	Weakly +	Weakly +

80	Gonorrhea 4 years ago; present attack of 8 months' duration	.....	.....	.....	.....	Medium +
81	Gonorrhea several times; present attack of 2 months' duration	.....	.....	.....	.....	Negative
82	First attack; duration of 6 months	.....	.....	.....	.....	Negative
83	Contracted gonorrhea 3 years ago	.....	.....	.....	.....	Weakly +
84	First attack; duration 3½ months	.....	.....	.....	.....	Negative
85	First attack; duration 6 months	.....	.....	.....	.....	Negative
86	First attack; duration 2½ months	.....	.....	.....	.....	Strongly +
87	Gonorrhea twice previously; present attack 3 months duration	.....	.....	.....	.....	Weakly +
88	First attack; duration 8 months	.....	.....	.....	.....	Negative
89	Gonorrhea several times; urine contains shreds	.....	.....	.....	.....	Negative
90	First attack; duration 5 months	.....	.....	.....	.....	Negative
91	Chronic gonorrhea; duration unknown	.....	.....	.....	.....	Negative
92	Gonorrhea 7 times in 12 years; duration of present attack unknown	.....	.....	.....	.....	Strongly +
93	Gonorrhea 4 years ago; duration of present attack unknown	.....	.....	.....	.....	Medium +
94	Gonorrhea 2 times previously; duration of present attack 2 years	Medium +	.....	Medium +	.....	Medium +
95	Gonorrhea 1½ years ago; present attack 5 months' duration	.....	.....	.....	.....	Negative
96	Gonorrhea 16 years ago; present attack of 9 months' duration	.....	.....	.....	.....	Negative
97	First attack; duration 1 year	.....	.....	.....	.....	Negative
98	First attack; duration 4 months	.....	.....	.....	.....	Negative
99	Urethritis for 12 years	.....	.....	.....	.....	Negative
100	Chronic urethritis; duration unknown	.....	.....	.....	.....	Strongly +
101	Gonorrhea one year ago; pain in heel	.....	.....	.....	.....	Negative
102	Chronic recurrent urethritis	Negative	Negative	Negative	.....	Negative
103	Gonorrhea 2 years ago; duration of present attack unknown	.....	.....	.....	.....	Negative
104	Gonorrhea 2 years ago; slight morning discharge	.....	.....	.....	.....	Negative
105	Gonorrhea 3 times previously; present attack 3 months duration	.....	.....	.....	.....	Weakly +
106	Gonorrhea 5 years ago; present attack 4½ months' duration	.....	.....	.....	.....	Strongly +
107	Gonorrhea previously; duration of present attack 6 months	.....	.....	.....	Weakly +	Weakly +
108	Gonorrhea 3 years ago; bilateral buboes	.....	.....	.....	.....	Negative
109	First attack; duration 15 months; had four inoculations of Gonorrhea Bacterin 1 year ago	.....	.....	.....	Negative	Negative
110	Chronic urethritis; duration unknown	.....	.....	.....	Negative	Negative
111	Gonorrhea for years; several recurrences	.....	.....	.....	Negative	Negative
112	First attack; duration 2 months	.....	.....	.....	Negative	Negative

TABLE 2.—Results with Respect to Serums Tested.—(Continued)

No.	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens				
		Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
113	Recurrent; duration at least 1 year	.....	.....	.....	.....	Weakly +
114	Second attack gonorrhea 1 year ago; prostatitis and seminal vesiculitis treated for 1 year; practically cured at present	.....	.....	.....	.....	Negative
115	Duration 6 months	.....	.....	.....	.....	Negative
116	Gonorrhea 4 years ago; recurrent prostatitis, seminal vesiculitis and stricture ever since	.....	.....	.....	.....	Weakly +
117	Gonorrhea 1 year ago and 5 months ago	.....	.....	.....	Medium +	Medium +
118	First attack of gonorrhea 1 year ago; never cured	Negative	.....	.....	.....	Strongly +
119	Gonorrhea 8 years ago; not treated; now has shreds in urine	.....	.....	.....	.....	Negative
120	Gonorrhea 6 years ago; discharge at present	.....	.....	.....	.....	Strongly +
121	First attack of gonorrhea 1 year ago; chronic posterior urethritis and prostatitis	.....	.....	.....	.....	Medium +
122	First attack of gonorrhea 3 months ago	.....	.....	.....	.....	Negative
123	Duration uncertain	.....	.....	.....	.....	Weakly +
124	Has had gonorrhea nine times; last attack 6 months ago	Negative	Negative	Negative	.....	Negative
125	First attack of gonorrhea 9 years ago; last attack 2 years ago	.....	.....	.....	.....	Negative
126	Duration unknown	.....	.....	.....	.....	Negative
127	Gonorrhea 3 years ago and continuously ever since	.....	.....	.....	.....	Medium +
128	Gonorrhea past 4 years; second attack	.....	.....	.....	.....	Negative
129	First attack of gonorrhea 5 years ago; never cured	.....	.....	.....	.....	Doubtful
130	Duration unknown	Medium +	.....	.....	.....	Strongly +
131	Gonorrhea twice before; present attack of 4 years' duration	Medium +	.....	Medium +	.....	Strongly +
132	Gonorrhea 9 months ago; discharged as cured from another hospital; still has shreds in urine	.....	.....	.....	.....	Weakly +
133	Duration one year	.....	.....	.....	.....	Negative
134	Gonorrhea five times	.....	.....	.....	.....	Medium +
135	Duration unknown	.....	.....	.....	.....	Negative
136	Gonorrhea four times; last time 8 months previously	.....	.....	.....	.....	Weakly +
137	Gonorrhea 4 years ago; last attack 2 months ago	.....	.....	.....	.....	Negative

138	Ten or twelve attacks of gonorrhea; last attack 6 months ago	.....	.....	.....	.....	Negative
139	Gonorrhea 2 years previously; shreds in urine	.....	.....	.....	.....	Weakly +
140	Gonorrhea one year ago	Weakly +	Weakly +	.....	.....	Strongly +
141	First attack; duration 1 year	.....	.....	.....	.....	Negative
142	Chronic hypertrophic changes in knee joint; prostatitis	Negative	.....	.....	.....	Negative
143	Gonorrhea for four years	.....	.....	.....	.....	Strongly +
144	Gonorrhea contracted 5 years ago; now has mild prostatitis and stricture	.....	.....	.....	.....	Negative
145	Gonorrhea 4 years ago; now has prostatitis and seminal vesiculitis	.....	.....	.....	Negative	Negative
146	First attack of gonorrhea 6 years ago; present recurrence one year ago (mild)	.....	.....	.....	.....	Negative
147	Duration unknown; has taken gonorrheal phylacogen without benefit	.....	.....	.....	.....	Medium +
148	Several attacks of gonorrhea over period of 10 years; had forty-four inoculations of gonococcic bacterin in 6 months 2 years ago	.....	.....	.....	.....	Weakly +
149	Same case 1 week later; under treatment	.....	.....	.....	.....	Negative
150	Gonorrhea 2 years ago	.....	.....	.....	.....	Negative
151	Gonorrhea first time 5 years ago; twice since; duration of prostatis 1½ years; three recurrences; last one 9 months ago	.....	.....	.....	.....	Negative
152	Recurrence of above case 2 months later	.....	.....	.....	.....	Negative
153	Gonorrhea 26 months ago; very slight; involvement of prostate; urine clear	.....	.....	.....	Negative	Negative
154	Duration unknown; case 155, 10 days after treatment	Negative	.....	Negative	.....	Negative
155	Gonorrhea 5 years ago	.....	.....	.....	.....	Weakly +
156	First attack; duration 6 months	.....	.....	.....	.....	Weakly +
157	Above case three weeks later	.....	.....	.....	.....	Weakly +
158	Gonorrhea 3 years previously	.....	.....	.....	.....	Weakly +
159	Gonorrhea 15 years ago; last 2½ years ago; premature ejaculation	Weakly +	Weakly +	.....	.....	Strongly +
160	Gonorrhea 7 and 2 years; present attack of 4 mos.' duration; had 5 injections of phylacogen	.....	.....	.....	.....	Medium +
	STRICTURE					
161	Gonorrhea 3 years and 4 months ago	.....	.....	.....	.....	Medium +
162	Gonorrhea 14 and 12 years ago	Negative	Negative	Negative	.....	Negative
163	Gonorrhea for 1½ years	.....	.....	.....	.....	Negative
164	Two attacks of gonorrhea; last one 18 months ago	Negative	.....	Strongly +	.....	Weakly +
165	Gonorrhea for 4 years with recurrences	.....	.....	.....	Strongly +	Medium +
166	Duration unknown	.....	.....	.....	.....	Strongly +

TABLE 2.—Results with Respect to Serums Tested.—(Continued)

No	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens				
		Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
		EPIDIDYMITIS				
167	Duration three weeks	.....	.....	.....	.....	Negative
168	Same as 167, two weeks later	.....	.....	.....	.....	Weakly +
169	Epididymitis 2½ months ago; still unresolved; prostatitis	.....	.....	.....	.....	Medium +
170	First attack of gonorrhea; duration unknown	.....	.....	.....	.....	Medium +
171	Gonorrhea and epididymitis 2 years ago; second attack at present	Weakly +	Weakly +	.....	.....	Strongly +
172	Gonorrheal history; slight swelling of epididymis	Negative	Negative	.....	.....	Medium +
173	Previous attack of gonorrhea; present attack of six weeks' duation	.....	.....	.....	.....	Medium +
174	Gonorrhea three or four times; last time six weeks ago	.....	.....	.....	.....	Weakly +
175	First attack of gonorrhea; duration six months	Negative	Weakly +	Strongly +	.....	Strongly +
176	Gonorrhea twice previously; present attack of six weeks' duration	Negative	Strongly +	.....	.....	Strongly +
177	Acute attack of nine days' duration	.....	.....	.....	.....	Weakly +
178	Acute attack of seven days' duration; denies gonorrhea	.....	.....	.....	.....	Medium +
179	Gonorrhea three times previously; epididymitis 15 years ago, plus present attack	.....	.....	.....	.....	Strongly +
180	Duration two months	Strongly +	Medium +	.....	.....	Strongly +
181	Duration unknown	.....	.....	.....	.....	Medium +
182	Bilateral epididymitis, probably tuberculous; has pulmonary tuberculosis; gonorrhea 10, 5 and 2 years ago	.....	.....	.....	.....	Negative

183	Chronic hypertrophic arthritis; duration 1 year; abdominal section 3 years ago; no G. U. symptoms at present	.....	.....	.....	.....	Medium +
184	Arthritis knee for 10 years; urethritis for 6 months, since when knee has been worse	.....	.....	.....	.....	Weakly +
185	Multiple subacute arthritis; no history of gonorrhea	Weakly +	.....	Weakly +	.....	Weakly +
186	Arthritis both ankles; gonorrhea for 3 years; synovitis 3 weeks after gonorrhea	.....	.....	.....	.....	Weakly +
187	Duration 10 weeks	.....	.....	.....	Weakly +	Weakly +
188	Pain in left shoulder; no inquiry as to gonorrheal history	.....	.....	.....	.....	Weakly +
	GYNECOLOGICAL CASES					
189	Pain in right ovarian region; leukorrhea; dysuria; frequency	.....	.....	.....	.....	Negative
190	Eclampsia	.....	.....	.....	Negative	Negative
191	Puerperal sepsis	.....	.....	.....	Negative	Negative
192	Pelvic abscess; puerperal sepsis	.....	.....	.....	Weakly +	Weakly +
193	Abscess of uterine cornua; vaginal smear shows Gram-diplococci	.....	.....	.....	Negative	Negative
194	Abscess in cornua of uterus; delivered of dead fetus	.....	.....	.....	Negative	Negative
195	Leukorrhea; dysuria; frequency	.....	.....	.....	Negative	Negative
196	Vaginal smear shows Gram-diplococci	.....	.....	.....	Negative	Negative
197	Vaginal smear shows Gram-diplococci	.....	.....	.....	Negative	Negative
198	Tenderness in hypogastrium; vaginal smear shows Gram-diplococci	.....	.....	.....	Negative	Negative
199	Tenderness in hypogastrium; vaginal smear shows Gram-diplococci	.....	.....	.....	Negative	Negative
200	Salpingitis	.....	.....	.....	.....	Negative
201	Pyosalpingitis	.....	.....	.....	Negative	Negative
202	Gonorrheal urethritis; salpingo-oöphorectomies	.....	.....	.....	.....	Medium +
203	Bartholinitis and cyst	Negative	.....	.....	.....	Negative
204	Gonorrheal endometritis	.....	.....	.....	.....	Strongly +

Reviewing our experience with the gonococcus complement-fixation test in general, it may be stated that a negative reaction is not decisive against the presence of a gonorrheal infection, and this is particularly true during the first six weeks of a primary acute urethritis either anterior or posterior in the absence of any complication, previous to which time we have never obtained a positive reaction; on the other hand, the supervention, even during the acute stage of the disease, of complications such as epididymitis, arthritis, prostatitis, etc., is prone to result in the production of a positive reaction. On the contrary in our experience, a positive reaction has been pathognomonic of a focus of gonococcal infection and has assisted many times in elucidating obscure or doubtful lesions. In fact, it appears that the gonococcus-fixation test enjoys greater specificity than does the Wassermann reaction, since thus far we have found no alien infection or condition capable of producing a positive reaction. This much certainly cannot be claimed for the Wassermann reaction. Moreover, there is no drug, as there is in syphilis, which is capable of causing the reaction to be negative during the existence of the disease. The probable explanation for the greater specificity of the gonococcus complement-fixation test rests in the fact that with gonococcic infections we employ a specific antigen—the gonococcus—while in the case of syphilis a non-specific or lipotropic antigen is employed.

The analysis of our cases further illustrates another interesting feature, namely, the persistence in some cases for a short time of a positive reaction, after an apparent clinical cure. This has occurred so often that we no longer discharge a patient cured or give him a clean bill of health so long as he gives a positive reaction, provided he has not been the recipient of immunotherapy. Usually a persistent positive reaction will become negative in two or three weeks following clinical cure with or without a continuation of treatment. The only explanation is that it requires an indefinite time for the antibodies, formed during the course of infection, to disappear from the blood. Torrey,[5] in animal experimentation, has found that the antibodies in immunized rabbits begin to disappear after ten days, and that the elimination is practically complete by the fiftieth day in all cases, disappearing much earlier in many instances. Thus a patient, evidencing a positive reaction two months after presumed clinical cure, should be regarded as still harboring a latent gonorrheal focus. Such experience, adopted either as routine procedure in the management of treatment, or discovered accidentally when gonorrheal infection or its symptoms were denied, or demonstrated by submitting suspected or positive syphilitic serum to the gonococcus-fixation test, has been encountered in a large number of cases.

Because of the generally acknowledged difficulties, at times, of differentiating the pelvic lesions in women, notably certain of the inflammatory

5. Torrey: Jour. Med. Research, 1910, No. 1.

from the cystic and neoplastic conditions, and also the differential diagnosis among gonorrheal, tuberculous and pyogenic infections themselves, the gonorrheal-fixation test seems destined to play a rôle. As in the male, in whom a positive reaction seems never to occur, at least so long as the infection is confined to the anterior urethra, so in the female we have been unable to obtain a positive reaction unless the disease has ascended to the level of the uterus.

An interesting, if not important, feature connected with this work is the comparative importance and value of the serological and bacteriological examination of cases of suspected gonorrheal infection. It is, to-day, a fact that the judiciary courts of our land require that the presence of the gonococcus be demonstrated, culturally, in order to establish its indisputable and legal identity. Based on this qualification, there are many cases of gonococcic infection impossible to determine, and we do not hesitate to state that, in our judgment, many such cultures are in reality the *Micrococcus catarrhalis* and not the gonococcus. This applies particularly to such isolation of the diplococcus of Neisser from chronic inflammatory processes. Moreover, it must be generally recognized that the demonstration of a Gram-negative diplococcus in smear is often insufficient and faulty evidence on which to base a diagnosis of gonococci. Therefore, it is most fortunate that in the chronic stage of the disease with complications, the complement-fixation test seems to be signally meritorious, while in the acute, subacute and frequently in the chronic forms of the diseases when the gonococcus may be demonstrated bacteriologically, the serological test promises little or nothing.

CONCLUSIONS

Detailed and careful analysis of the gonococcus complement-fixation test, performed with the serums of the cases tabulated in our series, would seem to justify the following assertions:

1. A positive reaction is invariably reliable and always denotes the presence of a focus of gonococcic infection.

2. A negative reaction frequently fails to determine the presence of disease especially in the acute and subacute stage when the disease is limited to the urethra, and never when it is confined to the anterior urethra or vagina alone.

3. In no alien non-gonorrheal infections of systemic disease has a positive reaction been obtained; the test, therefore, appears to be absolutely specific.

4. A positive reaction has been found to be present in 21.05 per cent. of patients clinically cured. Such patients, therefore, should not be discharged from treatment or observation until a negative reaction has been obtained.

5. Not infrequently, either when suspicious lesions are presented or accidentally, positive reactions will be discovered in patients denying gonorrhea.

6. In only 9.09 per cent. of cases of acute and subacute anteroposterior urethritis has the complement-fixation test resulted positively. The earliest appearance of a positive reaction in a primary attack of posterior urethritis, without complication, occured in the sixth week.

7. In a number of cases of chronic recurrent urethritis with acute exacerbations, the test was invariably positive; many of these patients undoubtedly had prostatitis.

8. The reaction resulted positively in one-third of all cases of chronic posterior urethritis; undoubtedly many of these cases had a mild or low-grade prostatitis.

9. In 52.08 per cent. of cases of chronic prostatitis a positive reaction was obtainable.

10. Two-thirds of all stricture cases demonstrated a positive test.

11. In epididymitis a positive complement-fixation test was observed in 87.5 per cent. of cases. If, from our series, one case probably tuberculous, may be eliminated, and a time duration of five weeks can be imposed, the positive result in this form of disease has been 100 per cent.

12. In arthritis, undoubtedly gonorrheal in character, positive reactions were obtained in 100 per cent. of cases.

13. In the diagnosis and differential diagnosis of pelvic disease in women, the gonococcus-fixation test is destined, unquestionably, to play an important rôle. We have been unable to obtain any positive results in uncomplicated urethritis, vulvovaginitis and Bartholinitis, and it would appear that the infection must ascend at least to the level of the uterus in order to produce a positive blood response.

14. Inoculations of gonococcus bacterin, antigonococcic serum, etc., may in themselves by the production of immune bodies be causes of positive reactions. How long these immunizing effects may endure is unknown, but we have observed patients, treated by immunotherapy, who one year later demonstrated negative complement-fixation reactions.

15. Although the bacteriological demonstration of the gonococcus culturally is the only absolute method for its identification in chronic inflammatory processes, the method as a routine procedure is impractical and susceptible of many failures and fallacious results, so that the complement-fixation test is not only less laborious, but is productive of a higher percentage of positive findings.

16. Finally, we hope and trust that the complement-fixation tests in gonococcic infections, as the Wassermann reaction in syphilis, are demonstrating their reliability and value to the extent that they will be recognized as indispensable, so soon as the courts shall rule that each applicant for marriage licensure must produce a health certificate properly attested.

A COMPARISON OF THE EXCRETORY POWER OF THE SKIN WITH THAT OF THE KIDNEY THROUGH A STUDY OF HUMAN SWEAT *

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BALTIMORE

The fact that the skin and the kidneys can act, to a certain extent, vicariously, seems to be generally accepted, as is manifest by the use of sweat-baths in the treatment of uremia. The skin excretes, qualitatively, practically the same substances which occur in the urine, namely, urea, ammonia, uric acid, amino-acids,[1] creatinin,[2] chlorids, phosphates, sulphates and certain enzymes.[3] The quantity of these substances, however, excreted by the skin is, normally, far less than that eliminated through the kidneys.

In health the ratio of the quantities of the various urinary constituents to one another is fairly constant, independent of the actual amounts of the substances eliminated by the kidney. Moreover, this ratio for urine differs from that existing between the same substances in the blood-stream. Hence the kidney exercises a selective concentrating action for certain substances. The question then suggests itself as to whether or not any such relation exists between the normal constituents of sweat, and, further, if any definite relation obtains between the quantities of the substances eliminated through the skin and kidneys. Such a similar relationship of the urinary and sweat factors would tend to show a similar selective power between the skin and kidneys.

Favre and later Kast[4] studied the relationship between the chlorids, phosphates and sulphates in the urine and sweat. The results show no outspoken relationship between the mineral constituents of the two fluids. These investigators found the ratios shown in Table 1 between these substances in sweat and urine.

Aliprando Moriggia[5] has noted the similarity of substances excreted both in sweat and urine, but showed the presence of an acid sweat in experimental alkalinuria in man, while in herbivora an experimental

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* From the Genito-Urinary Clinic of the Johns Hopkins Hospital and the Laboratory of Physiological Chemistry of the Johns Hopkins University.

* Submitted for publication, Aug. 7, 1913.

1. Embden and Tachau: Biochem. Ztschr., 1910, xxviii, 230.
2. Capranica, S.: Maly's Jahresb., 1882, xii, 190.
3. Gaube, M. J.: Compt. rend. Soc. de Biol., 1891, xliii (Addenda), 115.
4. Kast: Ztschr. f. physiol. Chem., 1887, xi, 501.
5. Morrigia, A.: Moleschott's Untersuchungen zur Naturlehre, 1876, xi, 129.

acid urine was always accompanied by alkaline sweat. This would tend to show some distinct selective power of the skin and kidneys, but is not conclusive, as the reaction of sweat may depend on the admixture of secretion from the sebaceous glands.[6]

TABLE 1.—CHLORIDS, PHOSPHATES AND SULPHATES IN URINE AND SWEAT ACCORDING TO STUDIES OF FAVRE AND KAST

	Chlorids	Phosphates	Sulphates	
Favre	1	trace	0.043	sweat.
	1	0.0959	0.380	urine.
Kast	1	0.0015	0.009	sweat.
	1	0.1320	0.397	urine.

W. Mironowitsch[7] found more mercury excreted in the sweat than in the urine after subcutaneous injection of mercury salt during treatment for syphilis. Argutinsky,[8] in an examination of two samples of sweat obtained by means of a vapor bath, determined the urea nitrogen, ammonia nitrogen and total nitrogen. The urea nitrogen amounted to 68.4 per cent. and 75.0 per cent. of the total nitrogen, and the ammonia nitrogen to 3.1 per cent. and 5.8 per cent. of the total. W. Camerer, Jr.,[6] in two cases found the urea nitrogen to be 34.6 per cent. and 34.0 per cent., and the ammonia nitrogen 8.0 per cent. and 6.6 per cent. of the total.[1]

J. H. Hoelscher[9] undertook a rather comprehensive study of the chemical composition of human sweat. His method of obtaining sweat consisted in wrapping the subject in sterile gauze, exposing to a dry heat of not more than 120 F. for a period of one or two hours, and then subjecting the gauze to pressure to obtain the fluid. The specific gravity, reaction toward litmus, total solids, organic and inorganic, urea and total nitrogen are reported, but the fact that the methods adopted for the analyses are nowhere mentioned considerably lessens the value of this work. Calculations which we have made from his data on the relationship between the urea nitrogen and total nitrogen of the sweat in twenty-four cases of normal passive sweat show the urea nitrogen to vary between 36 per cent. and 100 per cent. of the total. The majority of the values show a more constant relationship between urea and total nitrogen, but the extreme variation before noted is untenable. Moreover, his figures

6. Trumpy, D. and Luchsinger, B.: Arch. f. d. ges. Physiol. (Pflüger's), 1878, xviii, 494. Arloing, S.: Lyon méd., 1896, No. 50. Camerer, Jr., W.: Ztschr. f. Biol., 1901, p. 1271.

7. Mironowitsch, W.: Medic. Koje Obostenze, No. 12 (through St. Petersburg med. Wchnschr. Beilage, 1895, 39).

8. Argutinsky: Arch. f. d. ges. Physiol. (Pflüger's), 1890, xlvi, 594.

9. Hoelscher, J. H.: Jour. Am. Med. Assn., 1899, xxxii, 1352; N. Y. Med. Jour., 1904, lxxix, 296.

are higher in general than those which were obtained later by L. Riggs[10] and also by us.

Recently Riggs has made a short study of six normal cases and three nephritics[11] on the partition of the nitrogen of the sweat. The total nitrogen, urea and ammonia were determined, as well as certain inorganic constituents. We cite here the relationship existing between the ammonia nitrogen and urea nitrogen, as percentages of the total nitrogen, as presented in his report.

TABLE 2.—PERCENTAGES OF THE TOTAL NITROGEN[12] AS CALCULATED BY RIGGS

Urea Nitrogen	Ammonia Nitrogen
47.3	8.1
63.6	9.1
52.0	14.0
54.8	5.5
57.7	7.0
48.0	7.2

Tichborne claims to have detected uric acid in sweat obtained in a Turkish bath, using the murexid test.[13] Hoelscher states that uric acid is not a constituent of normal sweat. Riggs tested 400 c.c. of sweat according to Salkowski's method, but found no indication of uric acid or purin bodies. Uric acid appears to have been recognized as a constituent of pathological sweats, however; that is, in gout and rheumatism.[14]

In the course of this investigation, eight cases of normal passive sweat have been examined for uric acid and its presence demonstrated in each instance.

Our experiments have embraced a determination of the nitrogenous constituents only, with the addition of an estimation of the diastatic activity. The age and weight of the subject, the quantity of sweat eliminated in twenty-five minutes and the increase in body temperature during the procedure were noted in order to ascertain if any relation exists between these factors. The total nitrogen, urea nitrogen and ammonia nitrogen, with the addition of uric acid and diastase, in some specimens, were estimated. The normal values and relationship between

10. Riggs, Louis: Jour. Med. Research, 1911, xix, 285.

11. Although twenty-six analyses are reported on nephritic sweat, these specimens of sweat were in reality obtained from three patients who were subjected to repeated sweat baths.

12. This author has calculated the combined urea and ammonia nitrogen as percentages of the total, and has laid no emphasis on the percentages of the relative values here given.

13. Tichborne, C. R. C.: Brit. Med. Jour., 1887, ii, 1097.

14. Hammersten: Mandel Text-Book of Physiological Chemistry, Ed. 6, p. 800.

TABLE 3.—Chemical Determinations in Sweat Began Within an Hour After Obtaining the Sample

Case No.	Age	Weight	Appearance time	Duration minutes	Temperature before	Temperature after	Amount obtained c.c.	Specific Gravity	Reaction	Total N per cent.	Urea N Per Cent.	Ammonia N Per Cent.	Uric Acid Per Cent.	Diastase $D^{38}/_{24}$
1	23	220	30	25	....	.....	330	1.009	Acid	0.194	0.182	0.0159	.....	...
2	28	180	25	45	....	.....	102	1.009	Acid	0.136	0.077	0.0098	.....	...
3	22	165	20	25	98.4	99.8	50	1.007	Acid	0.067	0.033	0.0084	.....	...
4	20	185	20	25	98.0	99.6	93	1.011	Neutral	0.107	0.056	0.0056	.....	...
5	23	220	15	25	98.4	99.8	323	1.008	Acid	0.085	0.034	0.0073	0.00012	...
6	25	125	25	25	98.4	102.6	93	1.015	Acid	0.118	.....	0.0087	.....	...
7	20	175	20	25	98.4	100.6	190	1.009	Neutral	0.070	0.035	0.0053	.....	...
8	26	170	20	25	98.4	100.6	175	1.007	Acid	0.068	0.035	0.0070	0.00018	...
9	21	185	20	25	98.6	99.8	64	1.007	Acid	0.105	0.059	0.0094	.....	...
10	37	160	25	25	98.0	98.2	260	1.009	Neutral	0.069	0.039	0.0059	0.00014	...
11	22	178	30	25	98.4	101.0	120	1.009	Acid	0.175	0.102	0.0104	.....	...
12	24	175	20	25	98.2	100.2	420	1.007	Acid	0.059	0.031	0.0056	0.00009	...
13	25	190	20	25	98.2	98.8	196	1.008	Acid	0.090	0.041	0.0053	0.00014	1.1
14	34	190	15	25	98.5	99.8	270	1.007	Acid	0.055	0.026	0.0047	0.00010	1.0
15	22	185	15	25	....	.....	245	1.011	Neutral	.....	.....	.....	0.00005	2.1
16	23	165	20	25	....	.....	340	1.007	Neutral	.....	.....	.....	0.00007	1.0
17	28	210	20	25	98.2	98.8	80	1.009	Neutral	.....	.....	.....	.....	1.1
18*	22	190	20	27	....	.....	180	1.008	Acid	0.127	0.078	0.0115	.....	0.6
										.1016	.0955	.0085		

* During the procedure of sweating this case, 5 gm. of urea, dissolved in 100 c.c. of distilled water were injected by gravity intravenously, during a period of three minutes.. The blood and urine of the subject were collected immediately before and shortly after the sweating. No appreciable increase of the amount of urea present was found in either fluid after the injection.

these substances in blood and in urine are well recognized. Consequently, a comparison of the relationships with those of the sweat should prove instructive.

EXPERIMENTAL METHODS

Method.—The subjects chosen were normal male adults, living on a mixed diet, not rich in proteins. The cardiorenal and gastro-intestinal tracts were within range of normal, and none of the subjects were of neurotic type. The experiments were performed at approximately the same hour, about four hours after a breakfast, consisting of eggs, bread and coffee, no abnormal exercise having been indulged in in the interim. After rubbing the skin with 95 per cent. alcohol, the subject was placed in a rubber bag 7 feet long by 4 feet in circumference, on a simple wicker couch, the upper end of which was raised 8 inches. The bag itself was then caught up where necessary by large clamps to conform closely to the body of the subject, thus minimizing the air-space around him, and reducing the possible error of evaporation to a minimum. Above this bag, and surrounding it entirely, was a rubber-lined air-chamber, 1 by 3 by 6 feet, into the side and top of which was projected the mouth of a pipe 6 inches in diameter, conducting hot air. The end of the hot-air tube was protected below by a fan-shaped cuff of cardboard to prevent the possibility of heat being unduly concentrated. No water was given the subject immediately before sweating. Temperatures were taken by mouth at the beginning and end of the experiment. From the time of appearance of perceptible sweat, to the conclusion of the procedure an arbitrary period of twenty-five minutes was chosen, and in most cases this was amply sufficient to secure an amount of fluid large enough for all chemical investigation.

In every case the sweat was filtered through ordinary filter-paper to remove any cast-off epidermal débris. As used for investigation, it was a slightly opalescent liquid. Examination of several specimens microscopically gave no evidence whatever of cellular content. The chemical determinations were undertaken within an hour after obtaining the sample.

Methods of Analysis.—Specific gravity was estimated by hydrometer. Each sample was tested as to its reaction toward litmus paper. The total nitrogen was determined in the usual way by the Kjeldahl-Gunning method, the urea by the method recently developed by one of us for blood,[15] and the ammonia by the aeration method.[16] The uric acid determinations were made by the colorimetric method recently described by Folin for the estimation of uric acid in the blood,[17] using 100 c.c. to 200 c.c. for each determination. The diastase determinations were made by the method of Wohlgemuth.[18] The principle of this method depends on estimating the smallest quantity of the fluid to be tested which can completely change 5 c.c. of 1 per cent. starch solution (Kohlbaum's *Stärke löslich*) in twenty-four hours at 38 C., to products not capable of giving any blue color with iodin. In the case of sweat, owing to the small amount of diastase present, we have used a 0.5 per cent. or 0.25 per cent. starch solution, and referred the value to a 1 per cent. solution. That this procedure gives reliable results was determined by duplicate experiments, using larger quantities of sweat and a 1 per cent. starch solution. The diastatic activity of the urine and blood-serum was estimated by the same method. The values for diastase are expressed in terms of the number of cubic centimeters of a 1 per cent. starch solution which 1 c.c. of the fluid in question can change in twenty-four hours at 38 C. to products not capable of producing any blue color with iodin. This is designated as $D^{38}/_{24}$.

15. Marshall, Jr., E. K.: Jour. of Biol. Chem., 1913, xv, 487.
16. Folin: Ztschr. f. Physiol. Chem., 1902-03, xxxvii, 2261.
17. Folin: Jour. Biol. Chem., 1913, xiii, 469.
18. Wohlgemuth: Biochem. Ztschr., 1908, ix, 1.

RESULTS

Table 3 gives a general summary of the results obtained. A uniformity of the time necessary to produce perceptible sweat is evident. The figures cited would suggest that body-weight does not always effect a proportionate change in the amount of sweat or total nitrogen eliminated. Case 6 shows an amount of 93 c.c. and 0.1097 gm. of nitrogen eliminated for a body-weight of 125 pounds, while Case 3 shows an amount of only 50 c.c. and 0.0385 gm. of nitrogen eliminated for a body-weight of 165 pounds. No definite relationship apparently exists between the amount of nitrogen eliminated and an increase in body temperature during the procedure. Case 5 shows a very high output of nitrogen (0.2758 gm.) and no marked rise of temperature (99.8 F.), while Case 6 shows a comparatively lower output of nitrogen (0.1097 gm.) and a temperature of 102.6 F. Though this test was not carried out on the same subject, we feel that the observation is of value, as it is corroborated so many times throughout the table.

Although the absolute amount of any one constituent, normally eliminated, may vary between rather wide limits in different specimens, there exists a fairly constant ratio between the amount of urea, ammonia and total nitrogen excreted.

From the numerous investigations by Boland, Schultze, Camerer, Voges, Morner-Sjoqvist, Gumlich, Bodtker, Folin[19] and others on the relationship of different nitrogenous constituents to each other in normal *urine*, it is shown that the urea nitrogen amounts to from 84 to 91 per cent. and the ammonia nitrogen from 2 to 5 per cent. of the total nitrogen. The relation between the total nitrogen, urea nitrogen and ammonia nitrogen of *sweat* calculated from figures in Table 3 is shown in Table 4.

The urea nitrogen varies from 45.6 to 68 per cent. of the total, with a mean of 53.7 per cent.; while the ammonia nitrogen amounts to from 5.2 per cent. to 12.4 per cent. of the total, with a mean of 8.1 per cent. Hence it is apparent that the relationships between the different forms of nitrogen in sweat and urine are entirely different. In regard to the relationships existing between the various forms of non-protein nitrogen in *blood*, satisfactory data are far too scanty to draw any general conclusions. The urea nitrogen in normal blood amounts roughly to about 50 per cent. of the total non-protein nitrogen, while no apparent relationship between the amount of uric acid and urea or total non-protein nitrogen seems to exist.[20] The figures for uric acid show a very different relationship in sweat from that in blood and in urine, although the data are

19. Hammersten-Mandel Text-Book of Physiologic Chemistry, Ed. 6, p. 646 for a collection of the literature.

20. Folin: Jour. Biol. Chem., 1913, xiv, 33.

insufficient to tell whether or not any constant relationship exists between the uric acid and the total nitrogen of sweat.

The concentration of urea in blood is normally about 0.02 or 0.03 per cent. The kidney has the power of concentrating this about one hundred times, as the normal concentration in the urine is about 2 per cent. The sweat-glands can also concentrate urea, though to a much less degree, the concentration in sweat being about .05 to 0.3 per cent. Ammonia exists in extremely minute amounts normally in the blood, and in much greater concentration both in sweat and in urine; so both skin and kidney can concentrate ammonia. Uric acid exists normally in the blood in quantities ranging between 0.0007 and 0.0037 gm. per 100 c.c.;[21] in urine[22] between 0.015 and 0.080 gm. per 100 c.c., while in

TABLE 4.—PERCENTAGE OF TOTAL NITROGEN FOUND IN THE FORMS OF UREA NITROGEN AND AMMONIA NITROGEN, RESPECTIVELY

Case No.	Urea nitrogen	Ammonia nitrogen
1	68.0	8.2
2	56.6	7.2
3	49.7	12.4
4	52.6	5.2
5	46.6	8.5
6	....	7.4
7	49.9	7.5
8	51.5	10.2
9	56.0	8.9
10	55.9	8.4
11	58.3	5.9
12	52.2	9.5
13	45.6	5.8
14	47.3	8.5
18	61.4	9.0

sweat we have found only from 0.00005 to 0.00018 gm. per 100 c.c. From this it is evident that the kidney does normally concentrate uric acid, while in the passage of fluid through the skin its concentration is much reduced. The concentration in sweat is only about one-twentieth that in the blood.

Diastase, in general, may be said to occur in the urine in greater concentration than in the blood,[23] while the figures for sweat show a diastatic activity much lower than that of either blood or urine. Owing to the wide variation of diastatic activity of the blood, it was thought interesting to confirm this point by making diastase determinations on the blood, urine and sweat of the same subjects. The results show that,

21. Folin and Denis: Jour. Biol. Chem., 1913, xiv, 29.
22. Folin and Denis: Jour. Biol. Chem., 1912, xiii, 363.
23. Wohlgemuth: Biochem. Ztschr., 109, xxi, 381, 432.

although the kidney normally concentrates the enzyme, the latter is much less concentrated in the sweat than in the blood.

The urine was collected immediately before and after sweating, and the blood withdrawn from the arm immediately after emergence from the bag. The values show the amount in cubic centimeters of 1 per cent. starch solution, which 1 c.c. of the fluid can change to products not capable of giving blue color with iodin in twenty-four hours at 38 degrees.

TABLE 5.—DIASTATIC DETERMINATION ($D^{38}/_{24}$) IN URINE, BLOOD AND SWEAT.

	Urine		Blood	Sweat
Case No.	Before	After		
13	1,000	167	167	1.1
14	100	100	25	1.0
17	.....	166	25	1.1

COMPARISON OF THE EXCRETION OF DYES THROUGH THE SKIN AND KIDNEY

As far as concerns the excretion of non-toxic dye-stuffs through the skin, the following data show that the skin does not normally excrete the faintest trace of the substances used, which substances pass readily into the urine. Phenolsulphonephthalein was administered intramuscularly in 6 mg. doses in four normal individuals; the injection was made immediately before entering the bath, and the drug began to appear in the urine before the appearance of perceptible sweat and continued to be excreted after the sweating process was completed. In each of these cases the output of phthalein was normal in the urine, but not the slightest trace could be detected in the sweat even after concentration.[24] Experiments with methylene-blue were conducted in two ways. In one case, 8 grains were given in 4-grain doses, one hour apart, the last dose being given within thirty minutes of the time of appearance of perceptible sweat. Although the urine was deeply colored, both before and after collecting the sweat, no trace of methylene-blue could be found in the latter. In two other instances in which the subject had been given 12 grains of the drug per day for three days preceding the experiment, no

24. In a series of forty cases of universal skin lesions of all types, including dermatitis exfoliativa, psoriasis universalis, eczema, ichthyosis, etc., studied by one of us (Plaggemeyer), phenolsulphonephthalein was excreted by kidneys in normal amounts. This drug evidently has a decided selective action for the kidneys and is not, in any way, affected by concomitant skin lesions. Article to be published later.

color was obtained through the skin, though the urine both before and after the procedure was heavily pigmented.

Indigo carmin was administered by injecting 4 c.c. of a 4 per cent. solution into the gluteus maximus, thirty minutes before sweating. The urine showed a deep blue color, indicating a high output of the drug, while the sweat, which was definitely acid, did not show the slightest trace. Rosanilin given under similar conditions in another case also failed to be excreted through the skin.

Phloridzin was injected in 5 mg. doses and readily produced a glycosuria, but in the two cases examined no trace of glucose could be detected in the sweat with Nylander's test.

Hexamethylenamin was tried in two cases. In one, the patient was given 35 grains in a moderate amount of water within two hours of sweating, and in the other the patient was on a daily régime of 45 grains. Both cases showed a definite excretion through the skin, which may explain the pruritus occasionally present in patients on a urotropin régime.

SUMMARY

The facts shown by this study of sweat from eighteen normal cases may be summarized as follows:

1. Uric acid and diastase are apparently constant constituents of normal sweat.

2. Body-weight does not necessarily effect proportionate change in the amount of sweat eliminated nor in the total nitrogen content.

3. No definite relationship exists between the amount of nitrogen eliminated and an increase in body temperature during the procedure.

4. The relationships between the different forms of nitrogen in sweat and urine are entirely different. The concentration of urea in sweat is from three to ten times as high as that in the blood, but only one-tenth (1/10) the concentration of urea in the urine.

5. The sweat-glands have the power of concentrating ammonia, and the ratio of ammonia nitrogen to the total nitrogen is considerably higher than that in the urine.

6. Uric acid occurs in sweat in much smaller amounts than in either blood or urine, the concentration being about one-twentieth (1/20) that in blood and about one five-hundredth (1/500) that in urine.

7. Diastatic activity, though slightly variable in sweat, shows a mean value, lower than that in either blood or urine.

8. The commoner dye-stuffs used for colorimetric estimation of kidney function are not eliminated through the skin.

9. Phloridzin injections are followed by a negative sugar reaction in sweat, although the reaction is positive in urine, from the same case.

CONCLUSIONS

It has been demonstrated that no apparent relationship exists between the chlorids, sulphates and phosphates excreted in urine and in sweat, and it has been repeatedly shown that the kidney concentrates urea, ammonia, uric acid and diastase. Our study has demonstrated that the glands of the skin concentrate urea and ammonia, but that the diastatic activity is less than that in either blood or urine, and that uric acid is present in less concentration than in the blood. The relative concentrating power of the skin and kidney for urea and ammonia are very different, though in both cases the percentage values are higher than those for blood. These facts, in conjunction with the fact that the kidneys show a decided selective action for many dyestuffs, while on the other hand, mercury seems to be more readily excreted through the skin, lead us to conclude that, under normal conditions, the skin and kidneys show a distinct selective action. The bearing of this on sweat-baths as a therapeutic measure in cases of uremia and nephritis is evident. The various substances which are producing toxemia in a given case may be among those which the kidney can concentrate, while in sweat they are found in less concentrated form than in the blood-stream. In the former case, sweating would not be indicated. Hence, certain reservations should be made on the efficacy of such procedures as a routine method of treatment and much further work remains to be done on the relation existing between skin and kidneys in pathological conditions, accompanied by cumulative phenomena in the blood-stream; with especial regard to obstruction in the urinary tract.

We are greatly indebted to Dr. H. H. Young for the clinical material on which this study is based.

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STATUS LYMPHATICUS IN ADULTS, ITS CLINICAL DIAGNOSIS AND IMPORTANCE *

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At the present time our knowledge of the condition recognized as status lymphaticus, or as it is more commonly called by German writers — status thymicolymphaticus, is not based on etiology, but on physical characteristics.

It is not essential to the pursuit of clinical studies that we should have a theory of the disturbed physiology, which determines the abnormal physical individual, nor yet await the complete understanding of the separate or mutual functions of the various secreting tissues, before we admit the relation of the clinical findings to health and disease. What is important for the internist, and for the eugenist, is the recognition of a type of individual whose physical peculiarities seem to bear an important relation to his mortality, in certain infectious diseases, and to his susceptibility to some of the deteriorating influences which modern society tolerates or suffers from. This recognition of a type of person, who may not appear less healthy or less capable than the rest of society, is at present based wholly on physical examination, one may almost say, on inspection alone.

Inspection of the human body provides us with physical signs of health or disease on which we rely. The value of physical signs, in relation to health and disease, depends on the constancy of association of the observed facts during life with a definite series of findings after death.

If the physical examination reveal constantly certain variations from the usual, or the accepted normal, and if the post-mortem examination reveal a constant series of gross and microscopical abnormalities in a tissue or groups of tissues, then where these two sets of observations are noted in a high per cent. of cases among those dying of certain of the infectious diseases, we may presume that there is some causal relation between the physical findings and the mortality of such individuals.

From the time when Paltauf (1889-90) pointed out the pathological symptom complex of status thymicolymphaticus, pathologists have more and more generally verified his observations, and in some instances have added to the data he gave in defining the condition found post mortem.

* Submitted for publication, Oct. 1, 1913.
* Read before the Section in Medicine, Seventeenth International Medical Congress, London, Aug. 8, 1913.

When Neusser (1911) gave an equally clear description of the clinical picture of status thymicolymphaticus, an impetus was given to observations by the internists, to test their skill in establishing a reliable clinical diagnosis, with the possibility of its bearing on the prognosis or treatment of various diseases.

Having watched the cases of meningitis, typhoid fever, and septic infections in the general medical wards of Bellevue Hospital die apparently in a high percentage of cases when they showed the physical marks of status lymphaticus, and having noted at the autopsy table the constancy of pathological findings which confirmed the clinical description of such cases, I wished to test the reliability of the various criteria given for the recognition of a characteristic or classical case of status lymphaticus.

The material on which this study was based was at my disposal while attending the alcoholic wards at Bellevue Hospital in New York. These wards receive patients suffering from the toxic effects of alcohol and of other narcotic drugs, cases of attempted suicide and sick prisoners. Among the admissions are often to be found border-line cases, which, on further study, prove to be psychopathic cases rather than toxic individuals of normal mentality. One thousand cases were studied, five hundred consecutive male admissions in July and August, 1912, and an equal number in January and February, 1913.

The record of each patient consisted of the following points:

Age; country of birth; cephalic index, based on the occipitofrontal and biparietal diameters; the color and physical qualities of the hair of the head; the amount of hair on chin, the upper lip, on the chest in front, in the axillae, and the amount and distribution of pubic hair; the amount of faucial, lingual and pharyngeal lymphatic tissue, observed by inspection and digital palpation; the presence of palpable cervical, axillary and inguinal lymph-nodes; the shape and proportions of the neck, thorax, abdomen, thighs and upper arms; the details of the external genitals; the general nutrition; the presence of congenital anomalies; the clinical diagnosis.

Of the 1,000 cases examined, 780 were without any stigmata or physical characteristics which would mark them as abnormal.

Two hundred and twenty showed most if not all, of the physical attributes sufficient to identify them as cases of status lymphaticus.

Analysis of the records of these two groups shows certain facts.

As to age it was found that 18.63 per cent. of the status cases were under 30 years, while but 9.66 per cent. of the normal cases were under 30 years. Above the age of 30 the distribution of the status and of the normal cases showed such slight discrepancies as to lead to no conclusions. The patients' ages ranged from 19 to 84 years.

As to nationality or race the variations in the two classes were negligible. Eighteen nationalities were represented.

As to cephalic index, if we use the term dolichocephalic to represent an index of 80 or less and brachycephalic for an index of over 80, we find that the cases of status are almost equally divided, while the normal cases show a preponderance of 7 per cent. of dolichocephalics.

Status Lymphaticus, Per Cent.	Normal Cases, Per Cent.
Dolichocephalic, 49.14	53.63
Brachycephalic, 50.86	46.37

In noting the color, texture (i. e., fine or coarse), luster, curliness or straightness of the hair of the head, no differences of any importance were noted.

The beard was noted as being scanty in 9.87 per cent. of normal cases, but scanty or wholly lacking in 57.22 per cent. of the status cases.

Similarly it was found that the mustache was scanty in but 7.94 per cent. of the normal cases, but scanty or lacking in 55.90 per cent. of the status cases.

Sternal or anterior thoracic hair was found to be scanty in 41.15 per cent. of the normal cases, and scanty or wholly lacking in 89.54 per cent. of the status cases.

The axillary hair was scanty in 13.45 per cent. of the normal cases, but scanty or absent in 65.45 per cent. of the status cases.

The pubic hair was found to be of the feminine type (i. e., arranged transversely and not rising toward the umbilicus, but ceasing abruptly above the pubic region) in 13.20 per cent. of the normals, and in 95.90 per cent. of the status cases.

The faucial, lingual and pharyngeal tonsillar tissue was found increased in amount in the normal cases in 6.66 per cent., 26.02 per cent. and 4.48 per cent., respectively, and in the status cases in 7.27 per cent., 23.18 per cent. and 0.90 per cent., respectively; not notable differences except in the case of the pharyngeal tonsils. Even though the pharyngeal tonsil seems to be enlarged five times as often among status cases as in normal men, the percentage of incidence is too low to use for diagnostic purposes.

The case of the superficial lymph-nodes is somewhat similar, for although the cervical, axillary and inguinal nodes are found palpable in somewhat higher proportion of cases in the status individuals than among normals, the occurrence of such palpable glands in adults is so common as to allow of no diagnostic application of this point.

In normal cases the cervical, axillary and inguinal glands were palpable in 15.25 per cent., 33.33 per cent. and 53.71 per cent. respectively, and among status cases in 25.90 per cent., 41.81 per cent. and 55.90 per cent., respectively.

The neck was noted as long and slender in 32 per cent. of normals and in 36.81 per cent. of status cases—an unimportant difference.

The thorax was found long and narrow in 27.94 per cent. of the normal cases and in 44.09 per cent. of the status cases.

The contour of the abdomen as to its roundness or flatness showed no difference worth noting between the two classes.

The thighs were noted as rounded in 30.52 per cent. of the normal cases and arched in 13.97 per cent. of the normal cases, while in 75.46 per cent. of the status cases they were rounded and in 50 per cent. were arched. These terms, rounded and arched, are used to express the impression made by the difference between the masculine and feminine types of thigh, the rounded as contrasted with the flat thigh being characteristic of feminine physique, and an outward and forward bowing or arching being a feminine attribute as distinguished from the straighter masculine thigh.

In the case of the upper arm it was found that 25.76 per cent. of normal cases were described as having rounded arms, while among the status cases there were 75.90 per cent. with this feminine characteristic.

Among the normal cases the penis was noted as small in 22.56 per cent., while this was the case among the status cases in 51.83 per cent.

The glans penis was noted as small in normal cases in 26.03 per cent. and in status cases in 54.54 per cent.

The shape of the glans was described as pointed or acorn-shaped in normal cases in 32.05 per cent. and in status cases in 61.31 per cent.

There were no undescended testicles among the normal cases, but there were six cases or 2.7 per cent. found with undescended testicles among the status cases, four with both undescended, two with one undescended.

The size of the testicles was noted as small in 24.74 per cent. of normal cases, and among the status cases in 45.90 per cent.

As to general nutrition there were no differences of any moment.

Congenital anomalies were found in 0.25 per cent. of the 780 normal cases and in 3.63 per cent. of the 220 status cases.

Complicating medical affections, in addition to drug addiction, were found in 3.58 per cent. of the so-called normal cases and in 10.40 per cent. of the status cases; 94.4 per cent. of all cases were admitted for alcoholic intoxication.

To summarize the data obtained from these examinations, it may be said that 22 per cent. of the particular class of men representing chiefly the alcohol and narcotic drug habitués, show sufficiently striking variations from the usual masculine physical habit to be classed as cases of status lymphaticus; that, of the points usually noted in arriving at a diagnosis, those found to be constant enough to be entitled to considera-

tion are, scantiness or absence of hair on lip, chin, and in sternal and axillary regions, together with the feminine type of distribution of pubic hair with or without scantiness of pubic hair; a tendency to narrowness and length in the thorax; a noticeable roundness and arching of the thighs and roundness of the upper arms; small size of penis; smallness and pointed shape of glans penis and smallness of the testicles.

In addition, there is a physical character noted in a very large proportion of the cases, and present almost invariably when the points above summarized are also present, namely, a particularly velvety, or fine and delicate texture of the skin, which is seen and felt to be almost wholly free from the usual short hairs, to be found commonly, for instance, on the thigh in men. For lack of such terms as would accurately designate this quality of the skin, I have not made a record of its appearance in the cases above reported, but I wish to call attention to this as an important diagnostic point.

Of the points described by others as commonly noted in cases of status which I find of little or no value in arriving at a diagnosis are, the physical characters of the hair of the head, which is supposed to be commonly coarse and straight in status cases; the faucial, lingual and pharyngeal lymph tissue, which is supposed to be commonly increased; the superficial lymph-nodes which are supposed to be felt in a high proportion of status cases; the slender columnar neck and the rounded feminine abdomen which are reported as being usual in status.

In addition, there is a point, described by European observers, which I have so regularly failed to make on physical examination of status cases, and which has so little foundation in the experience of the pathologists at Bellevue Hospital, that I have not made it a part of my records, namely, the spleen. The spleen is supposed to be large in status. This I do not find to be the case.

I am permitted by the Director of the Pathological Laboratory to quote from the forthcoming hospital report the results of autopsy records of status since 1905.

Of the 3,600 autopsies, 288, or 8 per cent., were cases of status lymphaticus.

Of these 288 cases, 29.66 per cent. were recessive cases, as shown by microscopical as well as gross study of the lymphatic tissues of the body, and 70.33 per cent. were active cases. Twenty-six of the 288 cases (or 9.02 per cent.) were not associated with other demonstrable lesions as a cause of death.

Two hundred and sixty-two (or 91.08 per cent.) were associated with other lesions.

Of these 262 cases, 242 were associated with infectious diseases.

Epidemic, purulent, or tuberculous meningitis.

Typhoid fever.

Lobar pneumonia.

Acute and chronic pulmonary, and general miliary tuberculosis.

Acute and chronic cardiac infections.

Septic infections of a variety of origins.

It is to be particularly noted that of the autopsied cases of typhoid fever 23.07 per cent. were status. Of autopsied cases of acute infective endocarditis 19.51 per cent. were status, and of the autopsied cases of epidemic cerebrospinal meningitis 48.27 per cent., while of the autopsied cases of lobar pneumonia 2.96 per cent. were status; of tuberculous meningitis 3.80 per cent. were status; of acute and chronic pulmonary or general miliary tuberculosis 4.50 per cent. were status.

In arriving at a pathological diagnosis at post mortem the essential points to be observed in addition to those accessible to the clinician during life, are the gross and microscopic appearance of the blood-vessels, particularly the aorta, which is small, soft and elastic; the intestinal lymph adenoid tissues, the Peyer's patches and follicles, and the mesenteric lymph-nodes which are uniformly found enlarged; either a hyperplasia of the lymph follicles of the spleen in active cases, or fibroid tissue tufts which have replaced previous hyperplasia of the lymph follicles in the recessive cases; enlargement of the thymus gland out of proportion to the age of the subject in active cases.

It is true that percussion and possibly Roentgen ray examination will, in the hands of a few, elicit the presence of an enlarged thymus in children, but the likelihood of this decreases with every decade of the patient's age above the first. By deep digital palpation in the episternal notch the normal aorta can usually be appreciated at each systolic impulse, and this is rarely the case in status cases, owing to the small size of the aorta, but this is of little reliability in arriving at a diagnosis.

For the present it seems to me that a diagnosis of status lymphaticus is justified, when we find, in the case of a man, a decided scantiness of hair on chin and upper lip, scanty axillary and sternal hair, scanty or feminine distribution of pubic hair; the slender thorax; rounded contour of upper arms and thighs with an arching of the latter; hypoplastic external genitals, particularly if associated with cryptorchismus; and a delicate velvety skin. The diagnosis is further confirmed if we find hyperplasia of the lymph tissue of nose, throat and tongue and an increase in the palpable cervical and axillary lymph-nodes.

If we admit the justice of such a diagnosis, because of the confirmation of a sufficient number of cases verified post mortem, of what service will this prove in the practice of medicine?

The obvious and justifiable conclusion at present is that such individuals are more susceptible to the dangers of infectious diseases than

are normal people. To avoid for such people by all precautions, especially by artificial immunization, as for typhoid, diphtheria and meningitis, every chance of infection, is our evident duty. They are poor risks in an epidemic, and the prognosis for them, when they are infected, is more serious than for normal men. As they have passed the particular dangers of their state during childhood, by especial care or good fortune, so, during maturity, they are among those who cannot be expected to survive, as well as normal men, extreme fatigues, shocks, loss of blood, abuse of narcotic drugs or surgical procedures. Those physicians whose hospital experience is mainly with people of the upper walks of life, will undoubtedly find that the incidence of status lymphaticus is far below the figures I have presented here for alcoholic patients. And in the general medical wards of Bellevue Hospital, which receives almost exclusively the pauper class, the incidence is less than a quarter of that found among alcoholics.

Among psychopathic cases, particularly those who suffer acute alienation in the first three decades, the incidence of status is, I believe, even higher than among the cases I have reported above.

It should by no means be understood from this that all cases of status lymphaticus are undesirables, socially, as they may be physically less capable in the struggle for existence than their fellows, for it is in the experience of all who observe these cases that there are among them leaders in scientific and artistic professions, and men of the highest standards of character.

For the identification of status lymphaticus among women we rely on the peculiar character of the skin of the body and extremities, the scantiness of the axillary hair pad, the scantiness of pubic and perineal hair, hypoplasia of the genital apparatus, and particularly slender thorax and extremities. Some women of decided status conformity have a marked growth of hair on the face and upper lip. As has been pointed out by Paltauf, Bartel and others, the status cases among women are in a high percentage of cases subject to the dangers of pregnancy and the puerperium. With this addition, what has been said of male status cases applies equally to women.

While we await the embryological, or physiological, explanation for this particular physical habit (lymphatismus, hypoplastic constitution, constitutional inferiority, status thymicolymphaticus, or status lymphaticus), there is much which the clinician is equipped and particularly fitted to discover as to the relation between status lymphaticus and the incidence and course of various pathological states.

In closing, let me gratefully acknowledge my debt to Dr. Charles Norris, Director of the Pathological Laboratory at Bellevue Hospital, who was the first in the United States to recognize the clinical picture of status lymphaticus in adults, and place its diagnosis on a sound basis for clinician and pathologist.

Without his experience and records of the past seven years I could not have prepared this paper.

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BIBLIOGRAPHY

The list of references appended to the monograph of Bartel and Bauer in 1912, and the classical articles by Paltauf and v. Neusser make a further bibliography at this time unnecessary.

Bartel and Bauer: Status Thymico-Lymphaticus u. Status-Hypoplasticus, Leipzig, 1912.

v. Neusser: Zur Diagnose des Status Thymico-Lymphaticus, Wien, 1911.

Paltauf, A.: Ueber die Beziehung des Thymus zum plötzlichen Tod, Wien. klin. Wchnschr., 1889, No. 46, and 1890, No. 9.